

# AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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HOWARD C. TAYLOR, JR., and WILLIAM J. DIECKMANN

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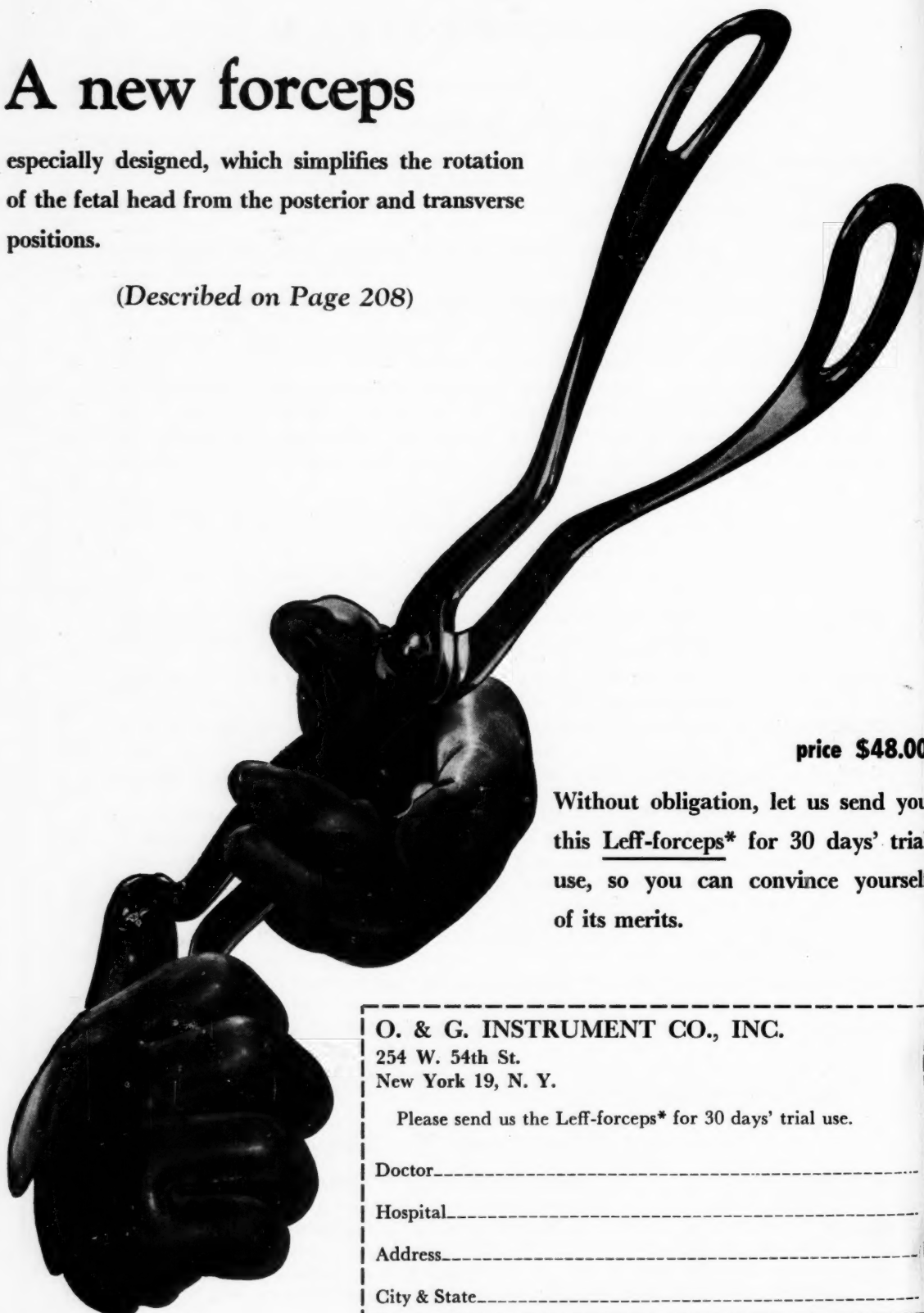
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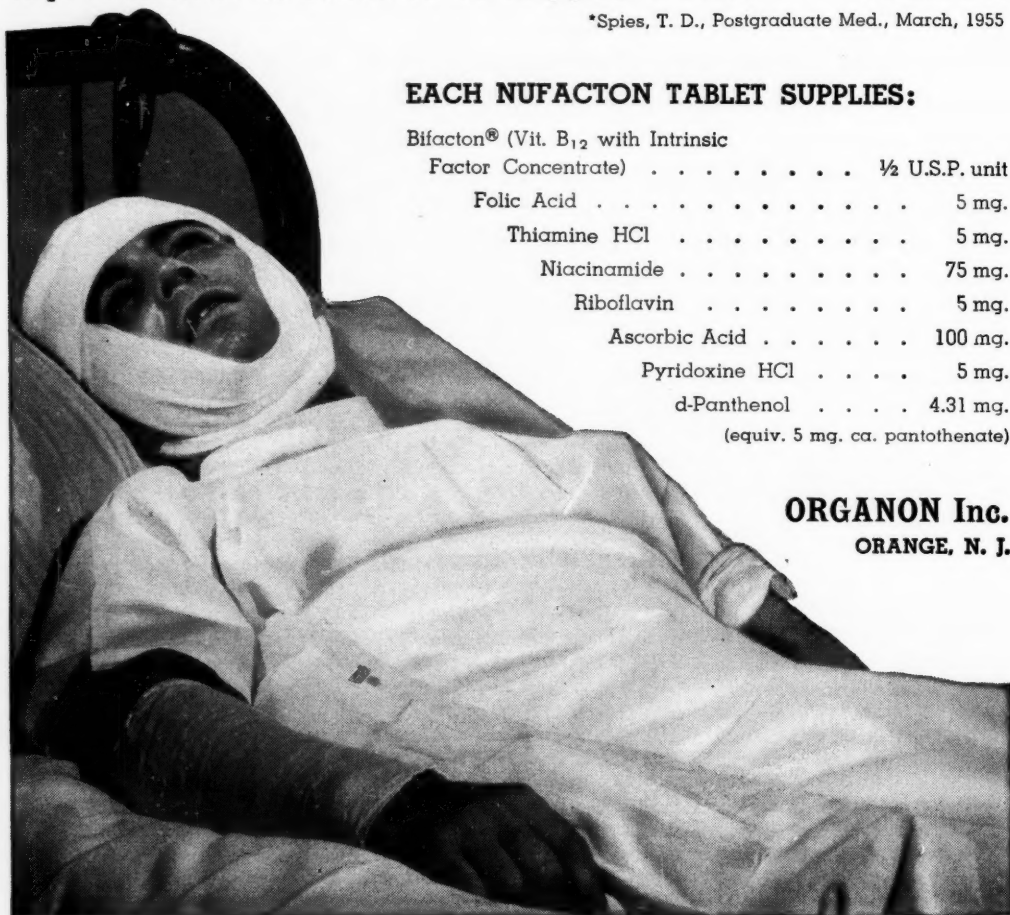
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# American Journal of Obstetrics and Gynecology

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## Original Communications

### **PARACERVICAL UTERINE DENERVATION BY TRANSECTION OF THE CERVICAL PLEXUS FOR THE RELIEF OF DYSMENORRHEA\***

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*(From the Department of Obstetrics and Gynecology, Tufts College Medical School,  
Cambridge City, and St. Elizabeth's Hospitals)*

**A**LGOMENORRHEA, or pelvic pain synchronous with menstrual bleeding, remains one of the most perplexing problems in gynecology. Usually referred to clinically as "dysmenorrhea," it is known to occur in two different main forms.

The pain of primary or essential dysmenorrhea usually occurs during very early menstrual life. It is crampy or colicky in type, localized usually to the low midline hypogastric area, and occurs synchronously with the actual onset of menstrual flow, although it may precede it for several hours. Its duration is usually several hours to two days. The pain of secondary or acquired dysmenorrhea usually occurs after several years of menstrual life, often not until the second or third decade. It is of a diffuse, dull aching character and may occur in one or both iliac fossae as well as in the midline. Occasionally, the pain radiates to the lower sacrum, or to the medial and posterior thigh or into the vagina. More often than not, it precedes the onset of menstrual flow by several days and persists during the flow for several days longer than the midline colicky pain, which may or may not accompany it.

Many young women suffering from primary dysmenorrhea are assured that marriage and childbearing will relieve the condition. Unfortunately, this does not always happen. On the contrary, the primary dysmenorrhea is not

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

infrequently aggravated by the sexual activity of married life, particularly if orgasm does not consistently occur. Even more frequently it is aggravated by childbirth. Moreover, patients who did not have primary dysmenorrhea often date the onset of their acquired dysmenorrhea to their marriage or to one or more childbirths. Not infrequently there is an associated infertility of either a primary or a secondary nature.

There has been a tendency to exclude the presence of organic disease from true primary essential dysmenorrhea and to insist that most acquired dysmenorrhea is associated with organic disease.

This is an unfortunate oversimplification not entirely consistent with the recorded facts. Ingersoll and Meigs<sup>1</sup> found endometriosis in 10 of 89 patients with primary dysmenorrhea who came to surgery at an average age of 24 years. Likewise Te Linde<sup>2</sup> found in a study of 243 patients with endometriosis that 51 per cent had primary dysmenorrhea; 19 per cent had primary dysmenorrhea which had become aggravated; whereas only 9 per cent had true acquired dysmenorrhea. Miller<sup>3</sup> has correctly stated, "The absence of a pathological condition recognizable only by present methods does not necessarily prove that one does not exist." There is a frequent association of acquired dysmenorrhea with the "pelvic autonomic syndrome" or "pelvic congestion" which Taylor<sup>4, 5</sup> believes to be a disorder of vascular physiology due to neurovascular imbalance of the pelvic autonomic nervous system.

Of the numerous theories regarding the cause of dysmenorrhea the most generally accepted is that the discomfort arises chiefly from hypercontractility of the uterine musculature due to an imbalance of its regulators, estrogen and progesterone.<sup>3</sup> Moir<sup>6</sup> ascribed the pain to ischemic anoxia of the myometrium secondary to the intense contractions which produced intrauterine tension much greater than that observed in labor. However, the steady ache, nausea, and vomiting seem inadequately explained on the basis of myometrial hyperactivity alone. There appears to be synergistic dysfunction existing between hormone regulators on the one hand and vascular and myometrial receptors on the other. A dual mechanism with myometrial hyperactivity giving rise to cramps and angiospasm causing a steady ache not only accounts for the variable discomfort characterizing dysmenorrhea, but also explains the capricious results of therapy. In any discussion of such a subjective problem as pain, one cannot deny the ever-present role of the psyche, both in the initiation and in the interpretation and emotional reaction to pain. Haman<sup>7</sup> has demonstrated that there is a lower threshold for pain in women with functional dysmenorrhea.

Practically all gynecologists agree that most primary dysmenorrhea will respond to sedation, rest, hygiene, and the production of anovulation either by estrogens or testosterone. These are less satisfactory remedies for the acquired type of dysmenorrhea. Hormone therapy, while effective, cannot always be accurately predicted, nor should it be carried on indefinitely. Altering normal menstrual function to remove only temporarily what is in reality a deep-seated symptom of psychogenic disturbance does seem rather futile. For practical purposes, it seems more desirable to raise the pain threshold, rather than to disturb the normal function of the ovaries by affecting an endocrine imbalance.

Temporary relief can usually, but not always, be obtained by prolonged dilatation of the cervical canal. The relief so obtainable is probably due to compression and injury of the cervical nerves rather than to the mechanical widening of the cervical canal itself. When the nerves regenerate, pain returns in most cases.

While it cannot be denied that there is a place for the resection of the superior hypogastric plexus<sup>8</sup>—presacral neurectomy—in the relief of primary dysmenorrhea, Novak<sup>9</sup> finds the usual percentage of success is only 60 to 70 per cent. The protagonists of the presacral neurectomy usually limit this procedure to those patients with uterine cramplike pain since experience has taught that the procedure is of little value in the alleviation of backache or of the diffuse, prolonged, dull pelvic ache of the secondary acquired type of dysmenorrhea. It is useless in the lateral type of dysmenorrhea, whether this be due to so-called ovarian dysmenorrhea (O'Donel Browne<sup>10</sup>) or parametrial dysmenorrhea as part of the pelvic sympathetic syndrome (Theobald<sup>11</sup>) or more properly pelvic autonomic syndrome (Taylor<sup>4, 5</sup>). Usually it aggravates menometrorrhagia (Davis<sup>12</sup>). Most advocates of the presacral neurectomy procedure now limit it to those patients for whom the production of an anovulatory cycle relieves the dysmenorrhea. Since not all patients with primary dysmenorrhea can pass this artificial test,<sup>1</sup> the indications for the procedure, even in primary dysmenorrhea, are becoming more limited.<sup>13, 14</sup>

Since dysmenorrhea is usually associated with menstrual periods wherein the endometrial biopsy reveals evidence of progesterone production, Ingersoll and Meigs<sup>1</sup> consider the relief of dysmenorrhea by the administration of estrogens to produce anovulatory cycles a prerequisite test for a hopeful prognosis. We agree with Kroger<sup>13</sup> that this test is not necessarily conclusive, for Israel<sup>14</sup> has shown that of 37 women with dysmenorrhea 13 showed no secretory changes in the endometrial biopsy. Accordingly, it seems hardly scientific or fair to relegate to a psychosomatic therapeutic nihilism those unfortunate women who do not happen to respond to the test of hormonal relief by the production of anovulatory menstruation.

The rigid test of any uterine denervation is the application of its technical procedure to the hard core of most difficult dysmenorrhea patients. These are the patients with acquired dysmenorrhea, whether or not there was antecedent primary dysmenorrhea. Often menometrorrhagia is present.

The relative inadequacy of the presacral neurectomy procedure in the relief of both primary and secondary dysmenorrhea is well known. In primary dysmenorrhea total failures after presacral neurectomy occur in 11 to 14.5 per cent of the cases.<sup>1, 15</sup> In acquired dysmenorrhea the total failure rate rises to 25 to 41 per cent of the cases.<sup>1, 15</sup>

Accordingly, the presacral neurectomy procedure has been virtually abandoned for patients with acquired dysmenorrhea at many clinics. Yet hysterectomy is a much more radical surgical solution for these young women. The late Victor Bonney<sup>16</sup> stated: "Radical extirpation of a uterus, tube or ovary which is functional or capable of having its function restored, is an admis-



sion of surgical defeat." This viewpoint becomes more important since any infertility associated with dysmenorrhea is often the more disturbing problem to the patient.

The importance of the role of the cervix in dysmenorrhea has recently been stressed by Reynolds<sup>17, 18</sup> who concluded that the cervix and the tissues adjacent to it are the site of uterine pain. Ingersoll and Meigs, White,<sup>19</sup> and others concede that the cervical nerve supply is not usually interrupted by the presacral neurectomy procedure. The cervical sensory supply runs in large measure with the nervi erigentes through the parasympathetic fibers reaching the cord via sacral roots 2, 3, and 4.<sup>1, 19, 20, 24, 33, 34, 35, 36, 37</sup> Lee<sup>20</sup> of London first described this important anatomic point in 1844 antedating Frankenhauser<sup>21</sup> by 20 years. Vara<sup>22</sup> in Finland and Te Linde<sup>23</sup> in this country have added resection down to sacral roots 1 and 2 as a part of their presacral neurectomy procedure.

We propose a simple procedure for denervating the uterus. The sensory parasympathetic fibers to the cervix and the sensory sympathetic fibers to the fundus traverse the cervical division of the uterovaginal plexus of Lee-Frankenhauser which lies in, under and around the attachments of the uterosacral ligaments to the cervix.<sup>45, 47</sup> An incision through the posterior vaginal fornix and the terminal 2.5 cm. of the uterosacral ligaments transects and interrupts not only the fundic but also the cervical sensory fibers. Such an incision interrupts the parasympathetic vasodilator fibers as well as the sympathetic vasoconstrictor fibers. Hence neurovascular imbalance is avoided. We call this procedure paracervical uterine denervation. The procedure may be done through the vagina or through the abdomen.

### Anatomic and Physiologic Considerations

That uterine pain could be relieved by transection of the uterosacral ligaments down to the top of the vagina is not new to European gynecologists. It has been done at laparotomy by Fraenkl<sup>24</sup> (1909), Brose<sup>25</sup> (1923) and Molin<sup>26</sup> (1929). It has been done vaginally by Ruggi<sup>27</sup> (1899), Jellett<sup>28</sup> (1900), Veit<sup>29</sup> (1910), Wagner<sup>30</sup> (1922), and Condamin<sup>31</sup> (1927). Jellett<sup>28</sup> transected the top of the vagina and drew the uterosacral ligaments forward and attached them to the anterior aspect of the cervix for the cure of retroversion of the uterus. He thought the relief of pain so obtained was due to the correction of the retroversion of the uterus. Fraenkl<sup>32</sup> interposed omental fat between the cut ends of the ligaments per abdomen. The interposition of living peritoneum to prevent regrowth of the nerves is the unique technical advance offered in this series of cases.

Recent anatomic and physiologic studies have clarified the neural pathways to the pelvic viscera. Labate<sup>33</sup> describes the derivation of the sympathetic components of the pelvic plexus as originating from the upper segments of the lumbar cord and from the lowest thoracic segments reaching the pelvic plexus by way of the superior hypogastric plexus which divides over the middle of the first sacral vertebra to form the right and left inferior hypogastric (presacral) nerves. Each of these nerves, 5 to 8 cm. in length, continues downward and laterally into the lateral rectal space where the pelvic or inferior hypo-

gastric plexus is formed.<sup>12, 33, 35, 37</sup> This is a large plexiform structure 3 cm. wide and 1 mm. thick intimately related to the uterosacral ligaments within the pararectal space posterior to the uterus and vagina.<sup>12, 33</sup> The pelvic plexus represents the focal point of distribution for the nerves to the uterus. It gives rise to subordinate plexuses, the cervical or uterovaginal being one of the larger subdivisions. Many microscopic nerve ganglia are found within this plexus<sup>33</sup> (Fig. 1). Some investigators<sup>21, 34, 36</sup> have described the presence of a large macroscopic ganglion which has been called the cervical ganglion of Frankenhauser.<sup>21</sup> Young<sup>35</sup> describes the uterine nerves as leaving those from the bladder and vagina just below the level of the pelvic plexus and passing as a thick bundle along the uterosacral ligaments to the cervix (Fig. 2) and thence to the isthmus and fundus of the uterus. Nerve filaments from the cervical or uterovaginal plexus accompany the uterine artery and its branches and are distributed to the cervix, corpus uteri, and proximal tubes.<sup>36</sup> A few of the sympathetic fibers course down the lumbar sympathetic trunk and pass directly to the pelvic plexus from the lateral sympathetic ganglia in the sacral region.<sup>12, 33</sup> At the cervical attachment of the uterosacral ligaments can be found the sympathetic fibers which have reached the cervix accompanying the uterine arteries.<sup>36</sup>

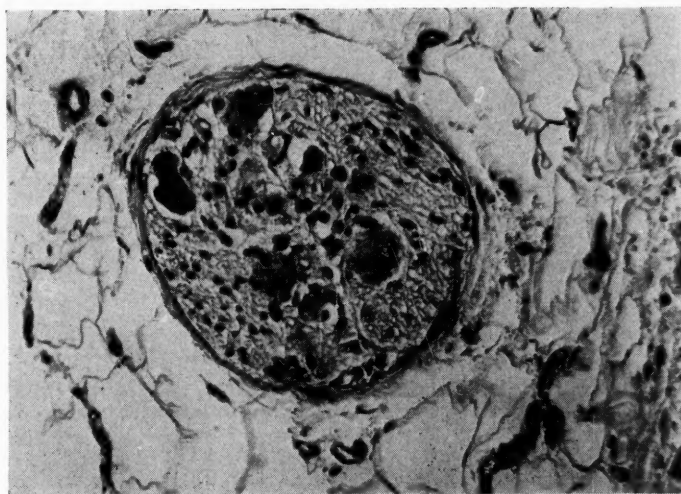


Fig. 1.—Autonomic ganglia and nerve fibers under uterosacral ligament 1.0 cm. from cervix.

The parasympathetic nerve components originate from the first to the third and fourth sacral nerves and reach the plexus via the pelvic nerves (*nervi erigentes*).<sup>12, 33, 35, 36</sup> Campbell<sup>36</sup> (1950), in a study of 33 cadavers, identified parasympathetic fibers in the anterior third of the uterosacral ligaments, confirming the demonstration of Latarjet and Roget<sup>34</sup> (1922) and Davis<sup>12</sup> (1933) of the intimate association of the uterine nerves with the uterosacral ligaments with a supply of small ganglia around the area of attachment of the ligaments to the cervix. In the uterus, the nerves accompany the blood vessels through the entire musculature to the basal layer of the mucosa.<sup>38</sup> Davis<sup>37</sup> (1938),



Fig. 2.—Nerves of cervical plexus ascending through three levels of uterosacral ligaments.



using a combined intra- and supravital methylene blue method, traced the majority of the nerves to their termination upon the capillary walls and also by way of spindle-shaped endings to the muscle fibers of the myometrium. At the internal os there are special pseudo-pacinian sensory corpuscles in the endocervix.<sup>39</sup> The nerves to the spiral arteries are distinct from those to the basal arteries.<sup>40</sup> The sympathetic component transmits vasoconstrictors and inhibitory visceromotor fibers as well as the sensory fibers from the fundus.<sup>12</sup> The parasympathetic component transmits vasodilator and excitatory visceromotor fibers<sup>41</sup> to the uterus as well as sensory fibers to the cervix and probably to the parametrium. It is doubtful that these nerves actively mediate the dilatation of the cervix.<sup>18</sup>

That the cervix has a different sensory nerve supply from that of the fundus was shown by the studies of Cleland.<sup>42</sup> He concluded that afferent impulses from the human fundus entered the cord at the eleventh and twelfth thoracic nerves; from the cervix, vagina, and perineum at the second, third, and fourth sacral nerves. He proved the accuracy of these conclusions by performing paravertebral bilateral blocks at T<sub>11</sub> and T<sub>12</sub>, thus relieving fundal pain of patients in labor. He then anesthetized the sacral nerves by caudal anesthesia as did Hingson,<sup>43</sup> producing relief of the backache and pelvic ache associated with labor. Ingersoll and Meigs<sup>1</sup> noted that backache was often unrelieved by the presacral neurectomy and concluded that the afferent nerve supply from the lower part of the uterus and cervix may pass outward through some other afferent rather than through the presacral plexus; that the parasympathetic supply to the uterus as observed from anatomic dissections was from the second, third, and fourth sacral segments. This impression was further confirmed by their inability to dilate the cervix without causing pain subsequent to presacral neurectomy, although the fundus could be curetted painlessly. The importance of the sacral parasympathetic fibers in the propagation of pain in pelvic disease has been stressed by White,<sup>19</sup> who noted that stimulation of the cervix or distention of the bladder and rectum still produces characteristic discomfort after presacral neurectomy which can be completely eliminated by sacral block or interruption by disease or injury of the lower sacral nerves.

The ovary receives its nerve supply from the ovarian plexus. This plexus arises from the intermesenteric and renal plexuses at the point of origin of the ovarian artery and consists of a fine network of nerve fibers which invest the ovarian vessels and follow these vessels into the infundibulopelvic ligaments for distribution to the ovary and distal part of the Fallopian tube. Some of the nerves of the ovarian plexus communicate with the fibers of the uterine plexus within the folds of the broad ligaments.<sup>23, 33</sup>

Granting, therefore, that some sensory components of the uterine nerve supply may pass up through the parametrium to go along with the ovarian plexus and thence to the renal and intermesenteric plexuses, it appears possible to transect most of the nerve supply of the cervix and the nerve supply of the fundus as these fibers pass through this focal anatomic area in, under,

and between (Fig. 3) the terminal 2.5 cm. of the uterosacral ligaments. Since both types of neurovascular and neuromuscular fibers pass through the same area, the procedure would leave the uterus in a state of autonomic balance, rather than set up a state of autonomic imbalance as the presacral type of denervation probably does. For the presacral type of uterine denervation, while it transects the vasoconstrictor fibers, leaves the nervi erigentes unopposed,<sup>12</sup> arising from S<sub>2</sub>, S<sub>3</sub>, and S<sub>4</sub> which contain vasodilator fibers to the cervix, fundus, and possibly part of the parametrium. This neurovascular imbalance (which, except by Davis,<sup>12</sup> Taylor,<sup>4, 5</sup> and Theobald<sup>11</sup> has been generally overlooked in the literature on uterine denervation) may underlie some of the hitherto unsuccessful results in the problem of acquired dysmenorrhea.

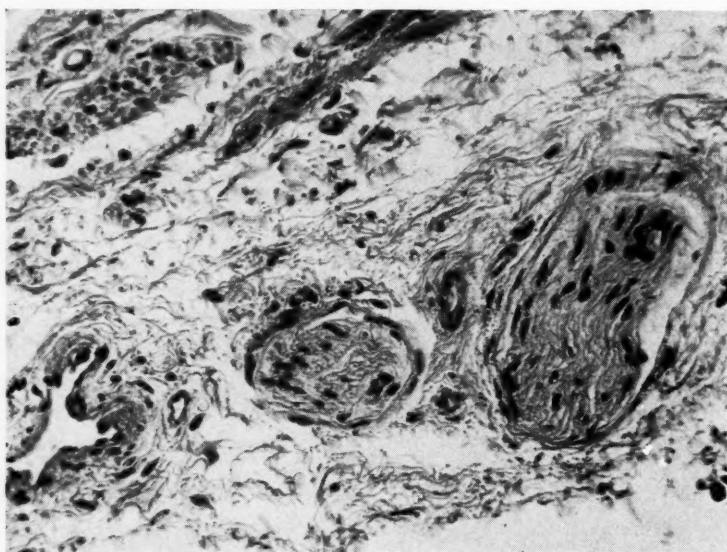


Fig. 3.—Autonomic nerves running with vessels in supravaginal fat beneath and between uterosacral ligaments.

#### **Surgical Technique of Paracervical Denervation**

We have previously reported the technique of uterine denervation per vaginam according to the method of culdotomy<sup>44</sup>—an incisional orifice in the posterior fornix of the vagina—with relief in 23 cases of dysmenorrhea.<sup>45</sup>

The procedure may be done either through the vagina or through the abdomen. Since the culdotomy approach is simply the first step of a vaginal hysterectomy, gynecologists may prefer the vaginal approach particularly if the illumination is improved by the use of the pelviscope set<sup>46</sup> which consists of a lighted right-angle retractor with twin lights at its tip and a set of 2 telescopes offering right angle or 45 degree angle fields of vision with a three-fold magnification. The general surgeon may prefer the abdominal approach. It has been our practice to reserve the vaginal approach for those cases of dysmenorrhea in which pelvic examination, both vaginally and rectally, revealed tenderness but no nodulation in the uterosacral ligaments and a cul-de-sac free of induration or masses. The vagina must be free of infection. In this series of 73 cases, the denervation was done by the vaginal route in 36 cases, by the abdominal route in 37 cases. In 2 cases, palpation of adherent

viscera through the intact peritoneum of the cul-de-sac after the vaginal incision had been made resulted in the election of the abdominal route.

*Technique per Vaginem.*—

The bowels are prepared by preoperative saline catharsis and enemas. The vagina is prepared by the usual cleansing douche and the insertion of a 100 mg. Terramycin suppository overnight preoperatively. A low spinal anesthesia or intravenous barbiturate is administered. The patient is placed in the lithotomy position and the vagina and vulva carefully scrubbed with Gamophen and soap. Zephiran aqueous solution is instilled into the vagina. The vagina is then wiped dry.

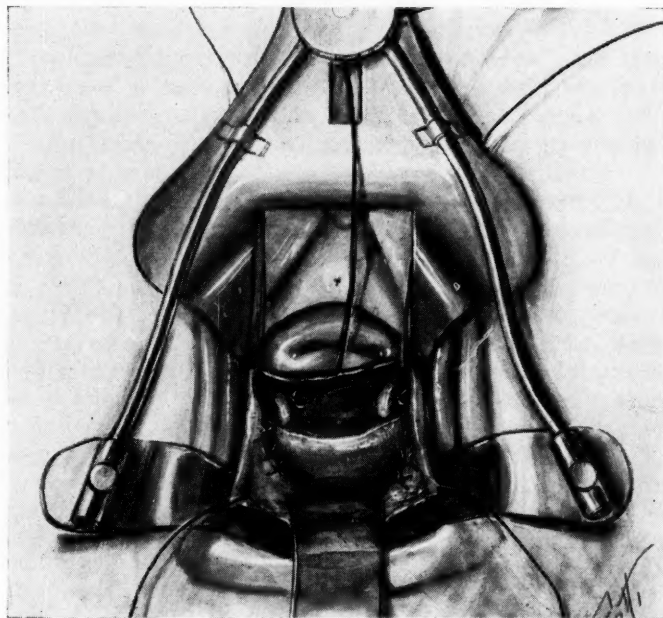


Fig. 4.—The uterosacral ligaments with the nerves have been ligated. The proximal stumps have been buried by simply suturing the peritoneum of the posterior cul-de-sac over them to the vagina.

The vaginal approach has been recently improved by the introduction of a new self-retaining vaginal retractor<sup>47</sup> which has a narrow base plate tilted so that it can be introduced against the anterior wall of the vagina beneath the arch of the symphysis without pressure on the urethra. Interchangeable side blades permit adequate lateral exposure within the vagina. The cervix is then grasped with a single hook and a suture is placed beneath the external os of the cervix through its posterior lip. This suture is held long and the cervix is drawn gently downward and forward. The end of this suture is then clamped around the knob of the self-retaining vaginal retractor. The apex of the vagina thus becomes more accessible.

Aspiration of the cul-de-sac by a hollow needle and syringe just beneath the cervix usually obtains peritoneal transudate. The posterior fornix of the vagina is incised transversely by scissors. With gauze over the index finger one can gently press downward on the lower margin of the transverse vaginal incision until the peritoneum is seen shining through the thin fascia which underlies the vaginal mucosa. The peritoneum is incised with scissors and the incision enlarged after gentle palpation of the bottom of the cul-de-sac by the



finger introduced through the orifice. Minimal trauma to the tissues at the bottom of the pelvis will ensue if one uses the suction tube for aspiration and dissection instead of gauze. The added illumination of the lighted retractor and the pelviscope permits direct observation of the pelvic viscera, the floor of the pelvis, and the area of insertion of the uterosacral ligaments to the cervix.

The presence of nonpalpable endometriosis, tuberculosis, or extensive adhesions in this area warrants abandonment of the vaginal route, even as it would if one were planning a vaginal hysterectomy. The presence of large uterine venous varicosities in this region has on only one occasion warranted the abandonment of the vaginal route for denervation.

The location of the ureters may then be visualized by the pelviscope with the right-angle lens system. Transillumination of the ligaments by the lighted retractor gives added reassurance.

The vaginal mucosa is next dissected off the lateral aspects of the uterosacral ligaments. A curved Heaney clamp then grasps the cervical attachment of the right uterosacral ligament. Another longer Heaney clamp grasps the entire width of the ligament 2.5 cm. below the upper clamp. With Mayo or Metzenbaum scissors the wedge of ligament and nerves is resected. Mattress sutures of No. 1 chromic catgut then replace the clamps. The same procedure is now done on the left uterosacral ligament. All the postcervical structures have now been divided, including the nerves of the cervical plexus of Lee-Frankenhauser.

To prevent regrowth of the nerves the posterior leaf of the peritoneal incision is bisected vertically and the mobilized segments are sutured over the ends of the proximal stumps of the uterosacral ligaments and firmly sutured to the submucosal fascia of the top of the vagina by fine silk or chromic gastrointestinal sutures (Fig. 4). The bottom of the cul-de-sac is then aspirated of all transudate. To prevent enterocele or retroversion of the uterus the uterosacral ligaments may then be drawn against the cervix and incorporated in the purse-string suture to close the peritoneum. The vagina is then closed by fine No. 000 plain catgut sutures. A vaginal pack is inserted for twenty-four hours to absorb any seepage from the incision.

#### *Technique by Laparotomy.—*

If endometriosis is thought likely or if gross abnormality such as fibroids can be felt, the abdominal route is preferred. After the associated pathologic abnormalities have been appropriately excised the uterosacral ligaments are brought upward by placing a suture just above the point of their insertion into the cervix. The suture is then drawn up around the turn screw of a Balfour self-retaining abdominal retractor. The uterosacral ligaments are then more easily visualized after the tension is thus placed on the cervical attachments.

The course of the ureters is then scrutinized. Rarely they lie close to ligaments. Usually they lie 1 to 2 cm. laterally.

Each ligament is clamped close to the cervix by a long, curved Ochsner or Heaney clamp. Another clamp is placed obliquely 1.5 to 2.5 cm. proximally and the intervening ligament resected deeply down to the top of the vagina. Mattress sutures now are placed in the cut uterosacral ligaments and the clamps are removed. The intervening peritoneum behind the cervix is then cut across. By blunt dissection with gauze pledgets aided by gentle vacuum suction the deep nerve fibers can then be visualized and transected down to the vagina both medially and laterally to the ligaments. Several small vessels may need to be clamped and ligated. The proximal uterosacral ligament stumps are then buried within the neighboring peritoneum. The interposition of living peritoneum as a barrier to regrowth of those nerves lying beneath the uterosacral ligaments poses considerably greater difficulty in the abdominal approach. By transecting close to the cervix in making the interligamentous incision, the free flap of



peritoneum over the posterior fornix is available for mobilization and suture against the top of the posterior fornix of the vagina covering the proximal uterosacral stumps.

If the uterosacral ligaments are taut and run snugly against the side walls of the pelvis, it is preferable not to excise a wedge but simply to transect them and sew the peritoneum with purse-string sutures over them. In the absence of endometriosis, the lateral peritoneum can be mobilized by blunt dissection of the underlying areolar tissue to avoid a "drawing sensation" at the time of the first menstrual period after the operation. We prefer to utilize the posterior and medial margins of the postcervical incision which do not produce tension so easily.

Since the uterine sympathetic nerves descending from the "presacral" or superior hypogastric plexus have now been interrupted close to the uterus, *there is no necessity of doing an additional presacral neurectomy*. Young<sup>35</sup> and Davis<sup>12</sup> have both demonstrated that the nerves to the uterus sweep up through the uterosacral ligaments, having left the nerves to the bladder in the pelvic plexus before entering the terminal fourth of the ligaments. For this reason, *the transection is usually done as close to the uterus as possible*. In cases where the transection was within 2.5 cm. of the cervical attachments, only 2 patients had any residual urine in the bladder (10 c.c. and 50 c.c., respectively) when tested on the third day after operation. There has been no difficulty in any case initiating micturition. Similarly, the rectal innervation appears to be avoided. Few patients even required a postoperative enema. None complained of constipation. Many reported more regularity and ease of defecation. Dyspareunia was relieved in 10 cases. No patient reported loss of orgasm. Five patients experienced their first orgasm after this procedure.

### Clinical Data

Seventy-three patients suffering from acquired dysmenorrhea were operated upon from Nov. 1, 1950, to July 1, 1954. In 35 patients there had been antecedent essential colicky dysmenorrhea which had become more intense and prolonged with the acquisition of a new element of diffuse pelvic ache usually referred to the iliac fossae and lower sacrum. In 38 patients acquired dysmenorrhea occurred after years of painless menstruation.

#### Marital Status.—

The marital status appears to be significant. Only 11 patients were single, whereas 37 ascribed the onset of their disorder to marital life. Of these 37 patients 26 were under study for associated infertility. Twenty-five women dated their complaint to childbirth. Of the latter group, 6 patients complained of aggravation of pre-existing dysmenorrhea, while 19 stated that they had previously had painless menses (Table I).

TABLE I. ONSET OF DYSMENORRHEA AND MARITAL STATUS

		PRIMARY AGGRAVATED	ACQUIRED
Single	11	9	2
After marriage	11	4	7
After marriage plus infertility	26	16	10
After childbirth	25	6	19

#### Age.—

The age incidence varied slightly (Table II). The average age at the time of the operation was 26 years for the primary aggravated group; 29 years for the acquired group.

TABLE II. AGE OF PATIENTS AT TIME OF OPERATION

AGE (YEARS)	PRIMARY AGGRAVATED	SECONDARY ACQUIRED
16-20	4	1
21-30	28	25
31-44	3	14

Three of the 4 patients under 20 had endometriosis of the uterosacral ligaments or cul-de-sac. The youngest was 16. The majority (53) of the patients were in the third decade of life and were anxious to have their childbearing function preserved or improved.

#### Results.—

During a four-year period, 85 patients with severe acquired dysmenorrhea were selected for paracervical denervation. Seventy-three were followed for four months to four years. Twenty-six of these were also under study for associated infertility. Only 6 were over 35 years of age. Fifty-three were under 30 years of age. The paramount importance of avoiding hysterectomy is obvious.

The majority of these patients had a dilatation of the cervix prior to or accompanying the denervation procedure. Some had had two or three previous dilatations. In the latter years of the study, however, unless uterine hypoplasia or stenosis of the cervix was suspected, this procedure was usually omitted so that the effects of the denervation per se could be better assessed. The use of pessaries within the cervical canal was omitted lest endocervicitis compromise subsequent fertility.

The results of the paracervical denervation procedure in the two classes of dysmenorrhea are represented in Table III.

TABLE III. RESULTS OF PARACERVICAL DENERVATION

TYPE OF DYSMENORRHEA	NO. OF CASES	RELIEF		
		COMPLETE	PARTIAL	ABSENT
Aggravated primary	35	30 (85.7%)	3 (8.6%)	2 (5.7%)
Acquired secondary	38	33 (86.8%)	3 (7.8%)	2 (5.2%)
Total	73	63 (86.3%)	6 (8.2%)	4 (5.5%)

All patients with partial relief considered the result satisfactory. They usually experienced mild cramps or markedly diminished pelvic ache. In no instance, where relief was complete, has there been a recurrence in from four months to four years. Of the four early cases in which unsatisfactory results were obtained by the vaginal route, one patient finally was totally relieved by a second denervation by the abdominal approach, at which time it was found that the right uterosacral ligament had been partially transected. Two other patients showed parametritis and ovarian adhesions to the cul-de-sac at the area of the insertion of the uterosacral ligament following unsuccessful attempts to relieve the pain by injection of 95 per cent alcohol per vaginam.<sup>12</sup> Bilateral ovarian endometriosis was subsequently found in the fourth case which preceded the use of the pelviscope.

#### Comment

Reynolds<sup>48</sup> states: "Except for the sensory aspects of uterine function every reproductive and sex function can be subserved without the agency of the nervous structures." After a careful survey of the literature he concluded that whatever the mechanism of dysmenorrhea the site of uterine pain is in the cervix and the tissues adjacent to it. The results we have obtained by transection of the Lee-Frankenhauser plexus in the paracervical tissues confirm

this opinion. Since the cervical nerve supply is interrupted, there is more consistent relief of backache in this series than that usually obtained with the presacral neurectomy procedure. The relief of lateral pelvic pain, which is probably the most striking result attained in the series, may be ascribed to the sensory denervation of the cervix or possibly to the sensory denervation of the parametrium as suggested by the results which European investigators<sup>12, 35</sup> obtained by the injection of Novocain and other substances through the posterior fornix of the vagina into the region of the uterosacral ligaments.

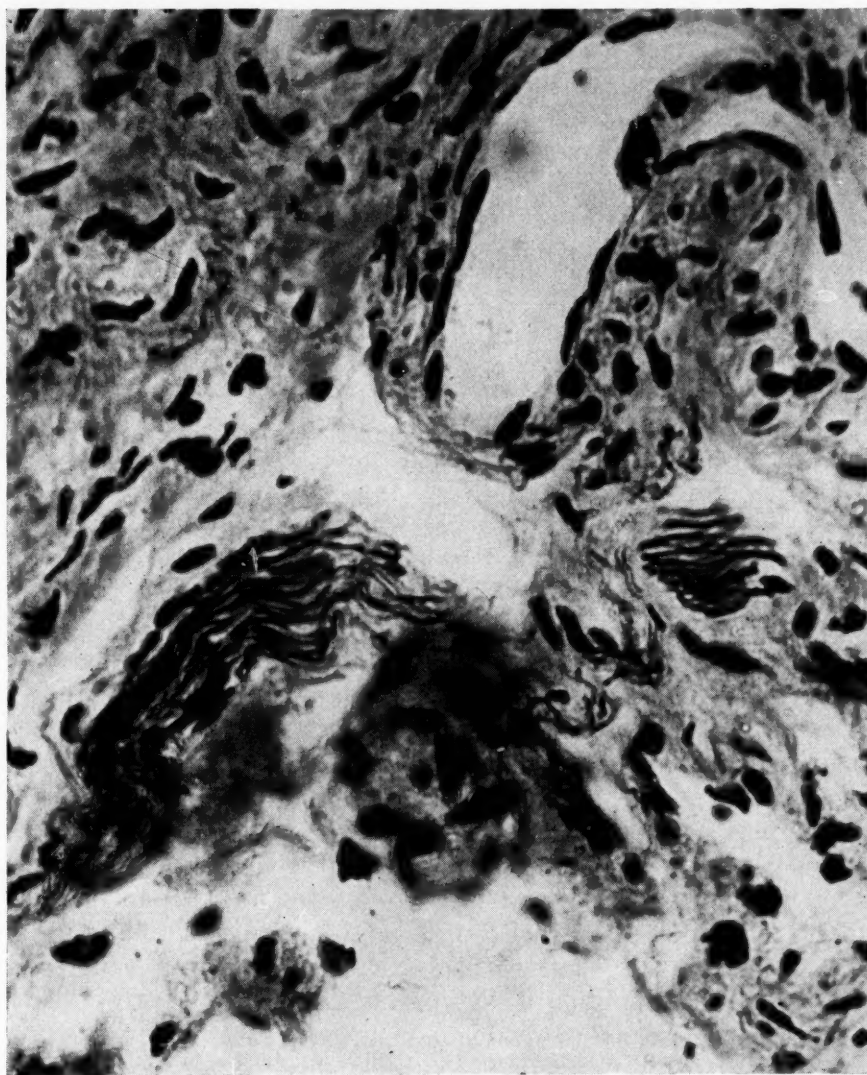


Fig. 5.—Autonomic nerves entering arterioles in uterosacral ligaments. (Bodian stain.)

That this denervation may have ameliorated a neurovascular imbalance involving the uteroparametrial-ovarian circulation is suggested by the remarkable relief of pain in those cases in the series which were associated with marked varicosities of the ovarian and the uterine venous plexuses. Hodgkin-

son<sup>49</sup> has recently calculated the enormous sixtyfold increase in the capacity of the ovarian pampiniform venous plexus as measured at the ovarian vein at full-term pregnancy. He has demonstrated the hypertrophy of the smooth-muscle fibers which implies an active physiologic role for these veins as a baffle mechanism in damping sudden high pressures. Patients with autonomic imbalance precipitated by the newer responsibilities of family life are not likely to be helped in the postpartum involution of the uteroparametrial vasculature by a surgical procedure such as presacral neurectomy which leaves the vasodilator fibers sweeping up through the uterosacral ligaments unopposed.

It seems likely that the relief that has been obtained in some of our cases is on a partially sensory and partially neurovascular basis. Many nerves end in the walls of small arterioles and capillaries in and between the uterosacral ligaments (Fig. 5). We have on two occasions seen rather large, dark veins at the uterovesical junction blanch out during the course of the denervation. On ten other occasions, the caliber of the large, dilated veins in the parametrium was observed to diminish. Further proof that uterine circulation is improved consists in the observation of the disappearance of cyanosis of the cervix gradually over a period of 2 to 4 months. Occasionally uterine cyanosis disappears during the operation. It is further suggested by the fact that in no case in the entire series was associated menometrorrhagia increased. Yet Davis<sup>12</sup> admits that presacral neurectomy often increases the flow in amount and duration and believes this is due to the action of the unopposed *nervi erigentes* from the sacral roots. With this type paracervical denervation which includes these *nervi erigentes* the blood flow at the menstrual periods, if previously excessive, was reduced by approximately one-half both in amount and duration. Normal menstrual flow was not affected.

Because of the wide anastomoses which exist between the uterine and ovarian venous plexuses, by way of the pampiniform veins, the release of high venous pressure in the parametrial venous system offers improvement of circulatory stasis in the ovaries. This explains the relief of ovarian and parametrial tenderness in the patients with lateral pain. Such an anatomic approach for relief of circulatory stasis is more logical than interruption of the infundibulopelvic veins, nerves, and ligaments as suggested by O'Donel Browne.

Moreover, the prompt aggravation of the dysmenorrhea in 3 patients within six months after presacral neurectomy was later found to have been due to the development of varicosities of the ovarian and uterine venous plexuses. On the theory that the presacral neurectomy procedure had produced a surgically conditioned autonomic imbalance leaving the "*nervi erigentes*" with their vasodilator fibers unopposed,<sup>12</sup> we finally obtained complete relief of the diffuse pelvic pain by transecting the parasympathetic vasodilator fibers according to the paracervical denervation technique. Taylor's<sup>5</sup> unsuccessful attempts to relieve pelvic congestion by presacral neurectomy may be on this basis. The relief of associated menometrorrhagia, the absence of postoperative congestive uterine bleeding, and the improvement of uterine cyanosis, all suggest that there is a secondary improvement in uterine neurovascular physiology.



The tendency to recurrence of symptoms, which is not infrequent after the presacral neurectomy, has not been seen in this four-year series. We believe this is due to that part of the technique which involves the interposition of living peritoneal tissue between the cut ends of the nerves, even though Bancroft<sup>50</sup> has shown that the capacity for regeneration of the sensory nerve fibers of the visceral autonomic nerves is less than that of the visceromotor fibers.

### Theoretical Physiologic Possibilities of the Procedure

Cannon<sup>51</sup> has shown that the denervation of a viscus produces more constant blood flow and increases delivery of hormones and sometimes increases receptivity of the tissues to hormones. Reynolds<sup>17</sup> insists that the uterine vasculature is essential for the effect of estrogen upon myometrium and endometrium. "No one," he states, "has ever shown that estrogen acts directly upon the excised uterus to initiate rhythmic contractility. Myometrial activity depends, therefore, upon a normally functioning vasculature." It appears to us sound therapy to provide maximal delivery of the endogenous ovarian hormones to the uterus by improving the uterine vasculature via denervation.

The clinical application of this type of uterine denervation to other research problems involving uterine circulation in obstetrics and gynecology seems logical. The problems of repeated premature labor, repeated separation of the placenta, repeated intrauterine fetal asphyxia, and repeated isoimmunization by Rh and A and B antibodies are presently under investigation in relation to uterine ischemia and will be the subject of later communications.

### Summary

1. The transection of the cervical division of the Lee-Frankenhäuser utero-vaginal plexus lying in, around, and under the terminal 2.5 cm. of the uterosacral ligaments permits sensory denervation of the cervix and fundus of the uterus and the proximal segment of the tubes.

2. The procedure may be done during laparotomy or culdotomy.

3. Neuromuscular and neurovascular autonomic imbalance is avoided since both sympathetic and parasympathetic pathways are interrupted.

4. Relief of acquired dysmenorrhea with or without antecedent primary dysmenorrhea was obtained satisfactorily in 69 of 73 cases (94.5 per cent). The relief was complete in 63 cases (86.3 per cent); in 30 of 35 aggravated primary dysmenorrhea cases (85.7 per cent); in 33 of 38 acquired secondary dysmenorrhea cases (86.8 per cent). Relief was partial in 6 cases (8.2 per cent). There were four failures (5.5 per cent).

5. There was no interference with the function of the bladder or rectum.

6. The regrowth of the nerves is prevented by the interposition of the posterior parametrial peritoneum between the transected uterosacral ligaments and the top of the vagina.

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## PROBLEMS ASSOCIATED WITH TREATMENT OF CANCER OF THE ENDOMETRIUM\*

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A REVIEW of the literature shows that there has been considerably less attention focused on adenocarcinoma of the endometrium than on other pelvic malignancies, especially carcinoma of the cervix. This is apparently due to the somewhat better prognosis assured by the slow rate of growth and late extension of fundal disease. In addition, the ratio of fundal to cervical malignancy in most clinics has been given as 1 to 8. It should be noted, however, that this ratio has changed in the past few years and recent reports indicate the ratio is approaching 1 to 1. It seems logical then to re-evaluate our methods of therapy at this time. The use of preoperative irradiation in the form of intrauterine radium followed by total hysterectomy and bilateral salpingo-oophorectomy in six to eight weeks has been advocated by many as the method resulting in the best survival rate. This study was undertaken to evaluate the use of radium in this manner.

Recently, multiple sources of radium in the uterine cavity have been employed by Arneson and others. The most commonly used method in many hospitals, however, is still the tandem source of 50 or 100 mg. capsules. These capsules are inserted into the fundus at the time of dilatation and curettage for diagnosis while awaiting an early report from the pathologist. That the placement of radium in this manner is grossly inaccurate is well known and is easily demonstrated as in Fig. 1. Here a 50 mg. capsule is placed well up in the fundus and skin clips are placed on the cervix at 12 o'clock and the lateral vaginal fornices to demonstrate the midline. This uterus was enlarged only two times and yet the capsule rests against the right wall, leaving the fundus and left wall out of the range of effective irradiation. The same situation pertains when 100 mg. is used in tandem. In Fig. 2, five 15 mg. tubes have been inserted into the fundus. X-ray shows the tubes to be bunched together in the left upper portion of the fundus, which may cause a "hot spot" in this area, especially in a thin-walled uterus, while the right lower portion of the uterus receives considerably less irradiation. Arneson was able to reduce the incidence of persistent tumor from 77 per cent using the tandem method to 29 per cent using the multiple-source technique in 32 patients. He points out the risk of uterine perforation with this method; advises hysterectomy in four weeks because renewed growth of the tumor occurs in six weeks; and states that radiation can produce enough necrosis of normal tissue to result in unrestrained growth of cancer.

\*Presented by invitation at the Joint Meeting of the Pittsburgh and Cleveland Obstetrical and Gynecological Societies, Pittsburgh, Pa., April 6, 1953.



It has frequently been observed that examination of the removed uterus following preoperative radium reveals viable carcinoma in many cases. The percentage of viable cancer varies from 50 to 75 per cent in most reports. The lowest was Arneson's 29 per cent and the highest was 84.4 per cent reported by Miller in cases following deep x-ray preoperatively. It should be noted that the deep x-ray was not given primarily to eradicate the site of origin, but was, nevertheless, ineffective in doing so.

To evaluate the usual method of preoperative irradiation, two empty capsules representing a total of 100 mg. of radium were inserted into the uterine cavity in a patient to be operated upon for a benign lesion. Skin clips were placed on the cervix, vaginal fornices, and various points in the pelvis. A No. 30 stainless steel wire was placed along the outer margins of the uterus from the fundus to the cervix. The uterine cavity was measured after the uterus was removed and outlined on the x-ray film. The lateral pelvic walls were identified by x-ray. On the basis of 5,000 mg. hr., the amount of radiant energy was calculated in gamma roentgens to each point using Quimby tables. The various pelvic points are shown in Fig. 3 and the data tabulated in Table I.

TABLE I. TOTAL GAMMA ROENTGENS DELIVERED TO THE VARIOUS PELVIC POINTS SHOWN IN FIG. 3 WITH THE USE OF TWO 50 MG. CAPSULES OF RADIUM IN TANDEM\*

Endometrium	E <sub>1</sub>	9,400 gamma r
Endometrium	E <sub>2</sub>	13,600 gamma r
Serosa	S <sub>1</sub>	2,200 gamma r
Serosa	S <sub>2</sub>	3,550 gamma r
Cervix	C	2,050 gamma r
Vagina	V <sub>1</sub>	2,950 gamma r
Vagina	V <sub>2</sub>	2,400 gamma r
Left pelvic wall	LW	1,500 gamma r
Right pelvic wall	RW	1,475 gamma r
Left ovary	LO	4,150 gamma r
Right ovary	RO	1,100 gamma r
Right infundibulopelvic ligament	RI	800 gamma r
Left infundibulopelvic ligament	LI	435 gamma r

\*Each capsule contained four 12.5 mg. needles with active length 1.35 cm. and 0.5 mm. platinum equivalent. The capsule had 0.5 mm. equivalent giving a total of 1.0 mm. Quimby tables are basis for calculations.

The uterus in this case was enlarged, thick walled, and contained several intramural fibroids. The endometrial cavity was only slightly distorted. The endometrium received 9,400 and 13,600 gamma r. Even though it is generally accepted that 6,000 gamma r is necessary to eradicate a tumor cell, yet, in this series of cases, 38 per cent of Stage I uteri revealed viable tumor following this type of irradiation. It seems, then, that more than 10,000 gamma r is necessary to destroy adenocarcinoma cells in the uterus.

If we keep in mind 10,000 gamma r as a cancerocidal dose and review the amounts in Table I delivered at various points throughout the pelvis, it becomes obvious why intrauterine radium so often fails to eradicate tumor in the myometrium, cervix, vaginal vault, and ovaries. In contrast, we were able to eradicate tumor cells at the lateral pelvic wall in patients with squamous-cell carcinoma of the cervix by using the combined energy of radium in the Ernst applicator plus deep x-ray to obtain 6,000 gamma r at the pelvic wall. We reached the

upper limits of safety in delivering this amount to the pelvic wall, however, so that it is probably impossible to deliver 10,000 or more gamma r to the lateral wall and not destroy the bladder and rectum or other important structures in the field of radiation.

Fig. 1.

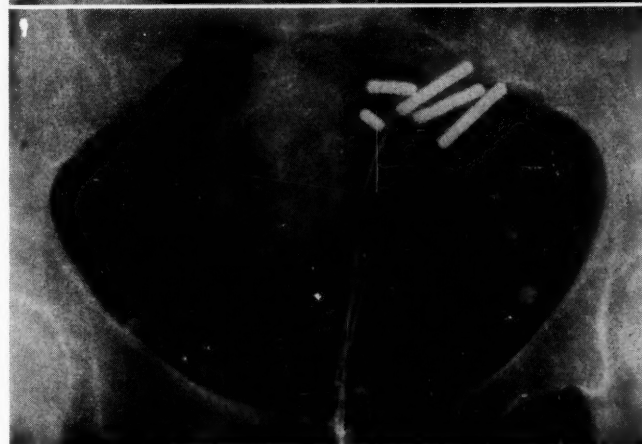
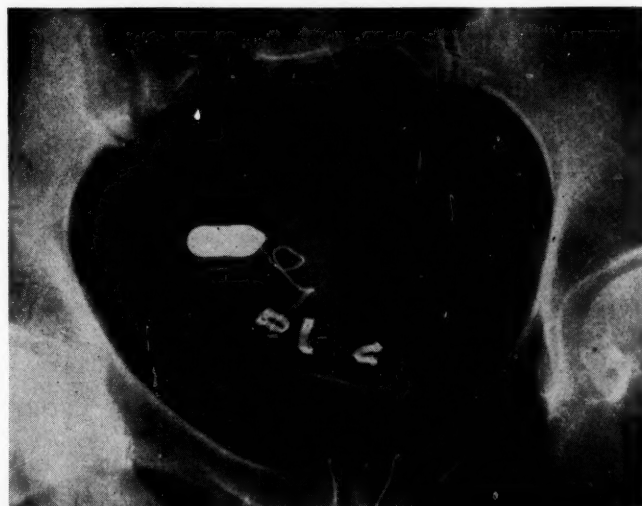


Fig. 2.

Fig. 1.—A 50 mg. radium capsule placed high in the fundus with skin clips on cervix and lateral vaginal fornices. Capsule rests in right side of uterus showing inaccurate placement.

Fig. 2.—Five 15 mg. tubes of radium inserted into fundus. X-ray shows the tubes bunched together creating a potential "hot spot."

It is also interesting to note the positions of the ovaries in Fig. 3. It appears that the right ovary received 1,100 gamma r while the left ovary received 4,150 gamma r. Both adnexa were freely movable in this patient and, as a result, these values are inaccurate since the position of the ovaries is seldom constant and undoubtedly changes with position of the patient, respiratory movements, etc. It is, therefore, doubtful that the ovary can be given a definite amount of irradiation unless it is firmly adherent to the broad ligament.

The vaginal fornices received less than 3,000 gamma r. It has been stated that the use of preoperative intrauterine radium will reduce the incidence of recurrences in the vaginal vault following hysterectomy. The protective effect of this small amount of irradiation is open to considerable question.

The use of radium is not without danger. The possibility of perforation, as mentioned in the multiple-source technique, is even present when one 50 mg. capsule is used, for, after surgical removal, some of the uteri, especially in the older age group, revealed a wall thickness of 0.5 cm. There is also the ever-present annoying cystitis and proctitis in a certain percentage of cases. It is possible that diagnostic curettage of the uterus in itself may spread the disease, so that additional intrauterine manipulation to insert radium, especially the multiple source technique, may enhance the possibility of further spread into the

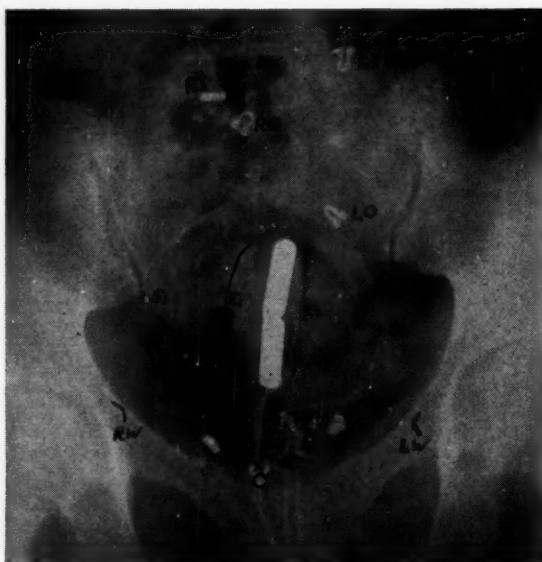


Fig. 3.—Two 50 mg. capsules of radium in tandem have been inserted into the fundus. Uterus has been outlined and important points identified (uterus measures 12 by 9 by 9 cm.; wall is 3.8 cm.). Amount of gamma roentgens to each point is then calculated, based on 5,000 mg. hr., and recorded in Table I.

lymphatics of the myometrium. In addition to the spread of tumor cells, radium may cause a rather severe reaction in the presence of necrosis and infection not infrequently found in the cancerous uterus. Finally, according to Speert, the use of radium preoperatively neither improved the five-year cure rate nor prolonged the interval of tumor recurrence in his series. Statistical proof to the contrary seems lacking.

Ninety-nine proved cases of adenocarcinoma of the endometrium treated at our hospital from 1940 to 1950, inclusive, were reviewed with the prime purpose of evaluating preoperative radium therapy. All other malignant lesions of the uterine body were omitted for this study. This series agrees statistically with other reports as to the incidence relative to age, race, parity, fibroids, diabetes, hypertension, and obesity. Particular emphasis was placed on the stage of the

disease, the method and amount of preoperative radium, the incidence of viable carcinoma following irradiation, and rate of recurrence in three years.

In each case the staging of the lesion was determined by the findings at operation and pathological study of the removed specimens. Several methods for staging adenocarcinoma of the endometrium have been suggested from time to time, but experience has shown that any clinical means of staging is even more inaccurate than our present concept of clinical staging of carcinoma of the cervix. The size or shape of the uterus seems to have little relation to the extent of the lesion. The small uterus may be extensively infiltrated with tumor. Enlargement of the uterus may be due to other causes such as fibroids which may involve as high as 40 per cent of these uteri or hypertrophy from prolonged estrogen stimulation either in the woman whose ovarian function continues beyond the age of fifty years or in one who has received "hormone shots" over a long period of time. Also, a fairly large symmetrical uterus may have most of the endometrium involved as a surface growth but no invasion of the myometrium so that the prognosis would be good even though the uterus is enlarged.

We, therefore, have chosen a modification of Finn's classification of stages as follows:

- Stage I Lesion confined to endometrium
- Stage II Myometrium involved
- Stage III Extension beyond myometrium but limited to reproductive organs (includes vagina, cervix, tubes, and ovaries)
- Stage IV Involvement of other pelvic organs or pelvic lymph nodes (bladder and rectum)
- Stage V Extrapelvic metastases (pulmonary, bone, etc.)

Since the disease can be staged accurately only at operation, its main value lies in determining prognosis and evaluating the best modality of therapy. There are two exceptions, i.e., a Stage III may be diagnosed by visualization and biopsy of cervical or vaginal extension and x-ray may diagnose Stage V with extrapelvic metastases such as bone and pulmonary lesions. The latter is most important, for such findings would preclude the advisability of surgery.

It seems reasonable to include all cases of involvement of the myometrium as the same stage (Stage II): Once the process has broken through the basal glands into the myometrium and its rich lymphatics, there is no statistical evidence that the prognosis is any better when 25 per cent of the myometrium is penetrated than when 75 per cent is involved. The remaining stages are based on most frequent sites of metastases and anatomical divisions.

The usual variations in methods of therapy in our hospital are shown in Table II.

TABLE II

METHODS OF THERAPY	NUMBER OF PATIENTS
Radium and surgery	44
Surgery alone	29
Radium alone	22
X-ray alone	4
Total	99



It will be noted that 29 patients were treated by surgery alone (these operations being performed by various surgeons). Sixteen of these did not have the advantage of a diagnostic dilatation and curettage prior to hysterectomy and hence were not operated upon on the basis of a proved diagnosis of carcinoma but only on suspicion or for some other reason. There were 7 patients treated by subtotal hysterectomy and in no case was diagnostic dilatation and curettage done prior to hysterectomy and, as a result, it must be assumed that the surgery was incomplete. In 2 cases, it is interesting to note that, following a proved diagnosis on dilatation and curettage, a vaginal hysterectomy was elected by the operator. It will be shown later that the selection of radium or x-ray alone in 26 cases was not a wise choice of therapy.

The follow-up on all cases is based on recurrence of tumor in one to three years rather than five-year survival rates. This method was suggested by Finn who stated that 85 per cent of recurrences were within three years and that only 5 per cent occurred in three to five years, the rate thereafter being about 1 per cent per year. Speert has shown the recurrence rate to be 49 per cent within the first year and 76 per cent within the first two years. The recurrence rate in our series was 90 per cent within three years. Our follow-up accuracy in this group is 95 per cent.

TABLE III. RADIUM AND SURGERY

STAGE	NO. OF CASES	VIALE CANCER IN UTERUS	RECURRENCE IN 3 YEARS	DIED IN 3 YEARS (PROBABLE RECURRENCE)
Stage I	21	8	1	1
Stage II	17	15	5	2
Stage III	4	2	1	0
Stage IV	1	1	1	0
Stage V	1	1	1	0

Table III gives data on the patients treated by preoperative intrauterine radium followed by surgery. In most cases the radium source was a 100 mg. tandem for a dose of 5,000 mg. hr. Each case was staged by the previously described method.

In 21 cases of Stage I, viable cancer was found in 8 uteri, or 38 per cent, following radium. In most of the specimens which showed no carcinoma, the growths were of the papillary or polypoid type, and in many there was no endometrial layer in the removed uterus, which seems to be evidence to support the idea that these lesions were either of the superficial low-malignancy type or the lesion was for the most part cured by curettage. One recurrence indicates the probable existence of tumor outside the area of surgery. In the Stage II group, it is shown that, in almost every instance of myometrial involvement, the radium failed to eradicate the lesion. The incidence of residual cancer was 88 per cent. The two cases free of residual cancer showed only very superficial involvement of the myometrium but were considered Stage II because the radiation necrosis extended into the myometrium. It is difficult to state whether the involvement was due to radiation only or whether there was tumor in that area prior to radiation. It is also noted that the recurrence rate is 29 per cent in Stage II.

In the Stage III group of 4 patients, there was residual cancer in 50 per cent but all 4 had involvement beyond the uterus. Certainly in these cases intrauterine radium failed to eradicate the lesions in the areas of extension. In this group, the recurrence rate was 25 per cent, similar to that in Stage II.

Stages IV and V were not benefited by either the radium or surgery, which in most of these patients consisted of a total hysterectomy with bilateral salpingo-oophorectomy.

Table IV demonstrates the results with surgery alone. As noted above, surgery was not always chosen because of a known diagnosis of carcinoma. It is of interest that there were no recurrences in this group except in Stage V where the surgery consisted only of exploratory laparotomy and biopsy. In this group, two patients were treated by vaginal hysterectomy after dilatation and curettage showed cancer. These were both Stage II cases and both patients survived for eight years or more. Had these patients received radium alone, it is quite likely they would both have had residual cancer and life expectancy would have been one or two years. Vaginal hysterectomy may well prove a useful procedure in the treatment of adenocarcinoma of the endometrium in the occasional patient over 70 years of age with a slow-growing early lesion who is a poor risk for abdominal surgery or whose obesity precludes the advisability of an abdominal operation. While certainly not the ideal method of surgery for this disease, its advantage outweighs the use of radium alone or other form of irradiation in these few poor-risk patients.

TABLE IV. SURGERY ALONE

STAGE	NO. OF CASES	RECURRENCE IN 3 YEARS
Stage I	11	0
Stage II	14	0
Stage III	1	0
Stage IV	0	0
Stage V	3	3

Table V shows the results when radium and x-ray are used alone. This group could not be staged because a laparotomy was not part of the treatment. The results, of course, are uniformly poor. Those without recurrence in three years presumably had a Stage I lesion and were probably cured by curettage. Two patients were not eligible for a three-year recurrence follow-up in this group.

TABLE V. X-RAY AND RADIUM

NUMBER OF CASES	RECURRENCE IN 3 YEARS	DIED IN 3 YEARS (PROBABLE RECURRENCE)
<i>X-ray alone.</i> — 4	3	1
<i>Radium Alone.</i> — 22	7	8

A comparison of the rate of recurrence of tumor in three years of patients treated by surgery alone, and those who received radium plus surgery, shows that 20.4 per cent plus a possible additional 6.9 per cent recurrence occurred in the radiated group, while in the group treated by surgery alone, only 3 had re-

currence or persistence of tumor and these were in the extrapelvic metastatic group. Fourteen of the radiated group, however, are not eligible for a three-year recurrence follow-up and 10 of the group who had surgery alone were not eligible. With this consideration in view, we may expect a few additional recurrences in both groups. Even though additional follow-ups will probably reveal recurrence in the surgical group, yet it will not alter the fact that more recurrences are seen in the group with preoperative radium. This interesting observation was also noted by Speert who found that the average recurrence time was twelve months when preoperative radium was used and two years with surgery alone. One might speculate that either the intrauterine manipulation for placement or the radiation itself may have a tendency to disseminate the tumor cells. Arneson commented that radiation may so damage the normal tissues in the tumor bed as to result in unrestrained growth of cancer rather than control.

From these observations, then, we are unable to validate the use of preoperative intrauterine radium. There is no definite evidence to support the idea that it actually eradicates tumor cells in Stage I cases and certainly it has not been lethal to tumor outside the limits of the endometrium. While our experience with the multiple-source technique is extremely limited, it is doubtful that sources of 10 mg. or less will provide a sufficient penetration of tissue gamma roentgens beyond the limits of the endometrium to deliver a cancerocidal dose in those areas even though the distribution may be more uniform to the uterine cavity. We are unable to find any other benefit from the use of intrauterine radium in these cases. It is our opinion that surgery consisting of total hysterectomy plus bilateral salpingo-oophorectomy following diagnosis by curettage has provided the best method of therapy for this disease in our clinic.

Recently, attention has been given to the lymphatic spread of carcinoma of the endometrium by Henriksen, Kimbrough, Finn, and others. In these reports, it is brought out that the spread is not very unlike the dissemination of carcinoma of the cervix by way of the lymphatics through the cardinal ligaments. It is not clear that the ovarian route is important, for Henriksen concluded that there is no constant pattern of metastases based on anatomic location of the lesion. The reason for this is the rich anastomosis of lymphatics in and around the reproductive organs. Meigs, in a personal communication, states that he does not believe that ovarian lymphatics via the infundibulopelvic ligaments play a role in the spread of adenocarcinoma of the endometrium. He also points out that the spread of the tumor cells is the same as in cervical carcinoma, i.e., by way of the lymphatics along Mackenrodt's ligaments to the lateral pelvic wall. In his series of 25 cases, the disease was limited to the fundus in 21 patients and, of these, 2 (or 10 per cent) had involvement of pelvic lymph nodes. Of the 4 remaining patients who had involvement of the endocervix, one (or 25 per cent) had lymph node involvement. The nodes involved were the obturators and iliaes. Randall reports an incidence of 20 per cent lymph node involvement in his series of 20 cases, and Finn emphasizes the importance of submucosal lymphatic spread as the cause of recurrence in the vaginal vault.

If we consider the apparent failure of preoperative irradiation, the occasional local extension, and the incidence of 15 to 20 per cent pelvic lymph node



involvement in this disease, it seems that a wider excision of the organs involved plus a pelvic lymphadenectomy would be of value in producing a higher cure rate. This method of treatment by radical surgery is being employed by McKelvey, Meigs, Randall, and others.

With these points in mind, we have established a plan of study. All patients admitted to our clinic who have menstrual irregularities at the age of 35 or over, and those who complain of postmenopausal bleeding or have a history of prolonged estrogen therapy are admitted for diagnostic curettage. In addition, patients who are to have a hysterectomy for some benign lesion routinely have a curettage of the uterus just prior to laparotomy. If the endometrium is unusual or suspicious, a frozen section is made of the curettings. This is done not to insert radium if there is malignancy, but to defer laparotomy so that the patient may have further study and be properly prepared for more extensive surgery.

If the curettings reveal carcinoma, the patient is studied for x-ray evidence of pulmonary and bone metastases; a cystoscopy and retrograde pyelogram, kidney function tests, and proctoscopic examination are made in addition to the usual routine laboratory examinations prior to surgery. The patient's physical condition is improved as far as possible by transfusions and antibiotics and preparation is made for a radical Wertheim-type operation combined with pelvic lymphadenectomy.

### Description of Operation

Unless there is some contraindication, continuous spinal and Pentothal anesthesia is preferred. A Foley catheter is placed in the bladder for continuous drainage. We have discontinued insertion of ureteral catheters preoperatively as we find that they are no longer needed as an aid in dissection and the added trauma to the ureters from catheterization adds to the postoperative urinary tract complications.

The preparation of the vagina consists of a thorough scrubbing with green soap plus the packing of the upper one-third of the vagina tightly with dry gauze. This is done to "seal off" the cervical canal and upper portion of the vagina which is to be removed at laparotomy. We do not suture the cervix because it is practically impossible to close the cervix tight enough to prevent escape of uterine secretions. The dry packing is more effective and also aids in identifying approximately the upper third of the vagina that is to be excised. The prevention of spill from the cervix is probably more important from the standpoint of infection than recurrence of tumor in the vaginal cuff, for there is reasonable evidence now that the recurrence in the vaginal cuff is due to submucosal lymphatic spread rather than surface dissemination of tumor cells at operation.

The abdomen is then prepared and a long suprapubic midline incision made beginning about two inches above the umbilicus. The lateral and anterior aspects of the aorta are explored by careful palpation up to the origin of the renal arteries. Special care is taken to rule out enlargement of the ovarian nodes which lie on either side of the aorta just below the renal vessels. All palpable nodes are removed and a frozen section made. If an ovarian or other aortic node contains cancer, the operation is limited to some palliative procedure such as hypogastric artery ligation for uterine bleeding, presacral neurectomy for pain, etc.

If there is no evidence of cancer above the bifurcation of the aorta, the procedure is begun by making an incision in the posterior parietal peritoneum

about two inches above the bifurcation of the aorta. Dissection is carried down to the wall of the aorta, then along the right common iliac, external iliac, and hypogastric vessels, removing all lymphatic and adipose tissue in and around these vessels. As the dissection proceeds laterally, the ureter is identified, gently lifted from its bed, with care to preserve its blood supply, and cleaned of adherent tissue. Slightly lateral to the ureter at the pelvic brim, the ovarian artery and vein are identified and with the use of a ligature carrier are doubly ligated and divided at the pelvic brim. The distal portion of these vessels and their accompanying lymphatic tissue are dissected out through the infundibulopelvic ligament to be removed later with the right adnexa. This procedure excises about 4 inches of ovarian vessels and accompanying lymphatics above the origin of the infundibulopelvic ligament before any manipulation of the uterus or adnexa takes place. The lymphadenectomy is completed on the right side of the pelvis, including removal of the obturator group of nodes, and the dissection of the ureter is continued through the broad ligament to the bladder.

Next the lymphatic tissue is removed, beginning at the bifurcation of the aorta and carried along the great vessels and ureter on the left. Here also, about 4 inches of ovarian vessels and lymphatics are removed, beginning at the pelvic brim, and dissection is continued through the left infundibulopelvic ligament. After the lymphadenectomy and ureter dissection are completed on the left side, the round and broad ligaments on each side are clamped and divided at the lateral pelvic wall. The uterine vessels are ligated lateral to the ureters and reflected medially as the distal portion of the ureter is dissected out. The bladder is reflected downward to the middle of the vagina and, with the aid of the packing in the upper one-third for identification, two Wertheim-Cullen clamps are placed across the vagina at this level and a transverse incision made distal to both clamps. We believe this method closes the vagina tightly and is the best method to prevent escape of uterine secretions. The remainder of the procedure consists of hemostasis and peritonization.

While the number of cases managed in this manner is quite small, we have had very few postoperative complications. The patients are discharged from the hospital on the fifteenth postoperative day. We have noted the usual hematuria for the first three days and mild cystitis and pyelitis. We believe it is very important to maintain a urinary output of 3,000 c.c. daily. The patients are up and about on the fourth postoperative day. It will take some time to collect a large enough series of cases to demonstrate the incidence of lymph node involvement and the effectiveness of this form of treatment for adenocarcinoma of the endometrium. We hope we can salvage the 20 per cent of cases that show lymph node involvement and hence reduce the recurrence rate in this disease.

### Comment

The insertion of radium sources into the uterine cavity is inaccurate as to placement and distribution. There is danger of perforation of the uterus and of spread of infection or tumor cells.

Five thousand milligram hours of intrauterine radium do not deliver enough gamma roentgens or "tissue" roentgens to important points in the pelvis to be cancerocidal.

A method of staging of adenocarcinoma of the endometrium is presented, based on operative findings and pathological study of removed tissue.

A review of 99 cases reveals residual carcinoma in 38 per cent of Stage I and 88 per cent of Stage II lesions following use of preoperative intrauterine radium. Tumor involvement of the myometrium was not affected by radiation of this type and the recurrence rate in the Stage II group was 29 per cent.

The lowest recurrence rate was obtained with surgery alone. Vaginal hysterectomy is superior to radium alone in a few selected poor-risk patients.

The results with x-ray and radium therapy alone were poor. The few cases presumably cured by this method may have been superficial lesions of low-grade malignancy or of the polypoid type with the curette being largely responsible for eradicating the tumor.

Surgery has proved to be the best method of therapy for this disease in our clinic. A more extensive operation is described and is being utilized in the hope that we will lower the recurrence rate in the 20 per cent of patients with pelvic lymph node involvement.

### Summary

An evaluation of the use of intrauterine radium in the management of adenocarcinoma of the endometrium is presented based on 99 cases. From this study, surgery is the treatment of choice. The technique of a more extensive operative procedure is described.

By employing this operation which includes pelvic lymphadenectomy, we hope to reduce the number of recurrences in patients whose disease extends beyond the limits of the uterus.

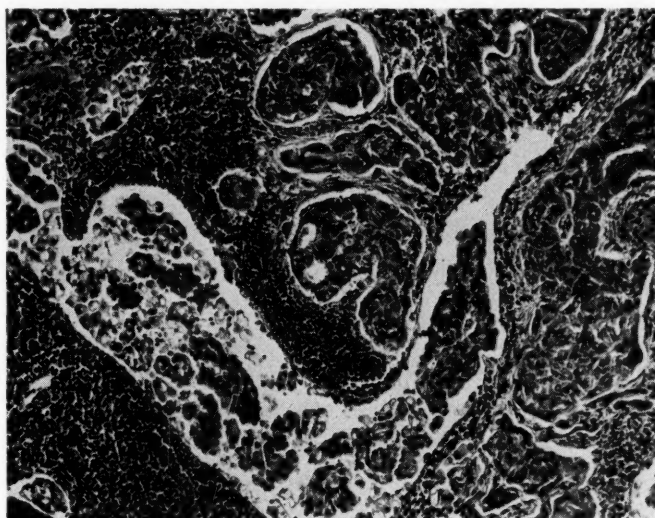


Fig. 4.—Metastatic adenocarcinoma in left external iliac lymph node. No other carcinoma was found outside the uterus.

*Addendum.*—Since the writing of this paper, patient M. T., aged 67, with the diagnosis of adenocarcinoma of the endometrium, was treated by the operation just described including pelvic lymphadenectomy. The tumor invaded the myometrium and was classified as Stage II. No carcinoma was found outside the uterus except in the left external iliac lymph node (Fig. 4).

This case demonstrates lymph node involvement which would be untouched by intrauterine radium or total hysterectomy or both, and requires a more radical approach if we hope to eradicate the tumor.

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## THE CYTOLOGICAL DIAGNOSIS OF CARCINOMA OF THE FALLOPIAN TUBE

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THE occurrence of cancer cells in the vaginal secretion with extrauterine malignancies of the female generative tract is very rare. If, however, definite malignant cells are evident in the smear and no tumor is found in the cervix or endometrium, the diagnosis of extrauterine malignancy must be considered.

Frech<sup>1</sup> in 1949 reported a case of primary adenocarcinoma of the ovary in which vaginal smears showed tumor cells, although there was no evidence of involvement of the endometrium. He emphasized that the cells seen in the smears fulfilled all the criteria for the diagnosis of adenocarcinoma.

Primary carcinoma of the Fallopian tube is rare. Renaud<sup>2</sup> in 1847 recorded the first primary carcinoma of the oviduct, but not until 1888 did Orthmann<sup>3</sup> note the first authentic case of primary carcinoma in this location. In 1889 Kaltenbach<sup>4</sup> described the primary bilateral carcinoma of tubes in a 50-year-old patient. Barth and Sanger<sup>5</sup> in 1895 gave the first detailed description and classification. In 1906 Orthmann<sup>6</sup> summarized 84 cases from the reports. The most outstanding of the reviewers were Vest<sup>7</sup> (1914), Laing<sup>8</sup> (1927), and Whorton and Kroch<sup>9</sup> (1929), this last publication bringing the number of recorded cases to 232.

In recent years there has been a rapid rise in the number of reports in this country, indicating that more careful attention is being given the disease and that there is a more accurate reporting of cases. Herbut<sup>10</sup> in 1950 noted that approximately 500 cases had been reported in all.

The incidence of these tumors as compared with other malignant tumors of the female generative system has varied between 0.16 and 0.45 per cent. The ages of patients whose cases have been recorded in the literature vary between 18 and 80 years. A majority of these have fallen in the 45 to 55 year group.

While primary carcinoma of the Fallopian tube often appears in combination with other pelvic lesions such as chronic salpingitis, ovarian cysts, or uterine myomas, there is no clear-cut evidence to indicate a predisposing influence on the part of any of these lesions. Grysta<sup>11</sup> in 1931 reported that one case of carcinoma of the Fallopian tube was associated with an ovarian cyst on the same side, the cyst being a simple unilocular one.

There are no characteristic physical signs or symptoms. Johnson and Miller,<sup>12</sup> however, have indicated a symptom in a woman who at or beyond the

menopause develops an acute blood-tinged or serous watery vaginal discharge which may or may not occur with severe persistent pain. In this case it may be discovered by bimanual examination that the uterus is not enlarged, but if an adnexal mass with or without a known cause is felt and if by curettage no pathology of the endometrium is shown, tubal carcinoma should be suspected.

The tumor has no predilection for any particular race. The disorder is unilateral in approximately two-thirds of the cases and bilateral in one-third of the cases. While any portion of the tube may be involved, approximately two-thirds of the lesions are located in the distal half of the organ and one-third of the lesions are found in the region of the isthmus.

The external surface of the Fallopian tube, even when the tumor is small, clings to adjacent structures by dense fibrous adhesions. In some instances the fimbriated end remains relatively normal. Occasionally it may remain patent although it contains soft, grayish-white, friable tumor tissue. The lumen may be more or less obliterated by dense overgrowth of fibrous tissue.

From the cytological viewpoint one might expect that desquamated tumor cells from the tubular epithelium would pass through the uterine canal and accumulate in the vaginal secretions. At this institution cells of adenocarcinoma were identified in the vaginal smears at the time of a postmortem examination of a case of primary carcinoma of the Fallopian tube. The tumor was identified at the fimbriated end of the tube.

### Report of a Case

On S. B., a 72-year-old white woman, there had been a follow-up at John Gaston Hospital over a period of seven years. The clinical diagnosis showed hypertensive cardiovascular disease. Since 1948 her blood pressure had been recorded as high as 230/128. She had done well until her last hospitalization when she was readmitted because of a sudden onset of severe dyspnea.

The patient was a gravida vi, para v; one pregnancy had terminated in spontaneous abortion. There was no history suggestive of pelvic inflammatory disease. Menstruation had ceased abruptly at the age of forty-six years. There was no history of postmenopausal bleeding or discharge. On physical examination the heart was markedly enlarged, and x-ray showed a particular preponderance of the left ventricle. There were loud, coarse inspiratory and expiratory râles throughout both lung fields. The patient died of congestive cardiac failure eighteen hours after admission without any response to treatment.

Postmortem examination was performed four hours after death. Routine cytological smears were taken from the cervix and endocervix. These were immediately stained by the Papanicolaou method, and the smears were examined before completion of the necropsy.

The cells were oval and stained deeply. They possessed rather large, round or oval, well-preserved nuclei. The cytoplasm was poorly preserved, and the nuclei were generally irregularly shaped. These cells arose from the deeper layers of the vaginal epithelium. All smears, however, showed definite malignant cells (Figs. 1 and 2).

At autopsy the heart weighed 520 grams. The valves and coronary arteries showed no abnormalities. The kidneys were fairly small and finely granular with a few coarse scars. Both lungs were quite heavy, and there was evidence of a marked chronic passive congestion. There was also a bilateral bronchopneumonia involving portions of both lower lobes.

The uterus measured 6.0 by 4.0 by 3.0 cm. The myometrium measured up to 1.6 cm. in thickness, and there were a few small nodules which were firm, measuring up to 1.5 cm.

by 1.0 cm. and showing the characteristic gross appearance of myomas. The endometrium and cervix showed no gross abnormalities. The right uterine tube measured 13.0 cm. in length with a diameter of 0.7 cm. at the proximal end. A few nodules measuring 0.1 to 0.2 cm. in diameter were noted on the serosal surface. The fimbriated extremity adhered closely to the adjacent ovary and showed an oval, irregular mass measuring 2.3 by 0.7 by 0.5 cm. (Fig. 3). This mass was grayish white and friable. The tube was patent throughout.

Fig. 1.

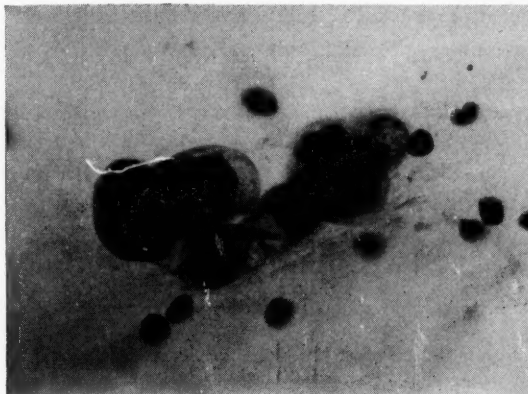


Fig. 2.

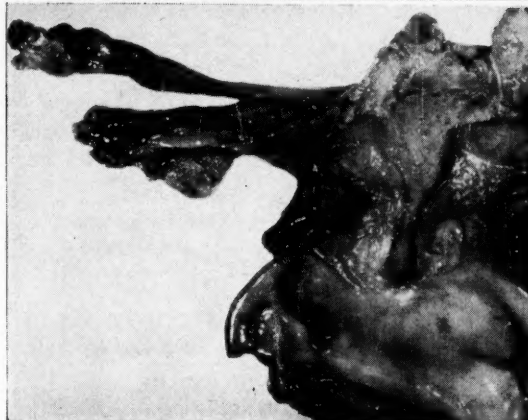
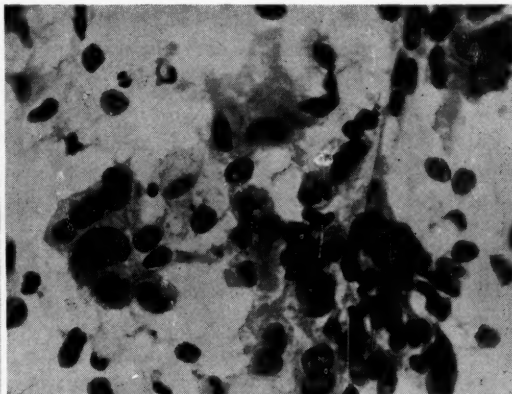


Fig. 3.

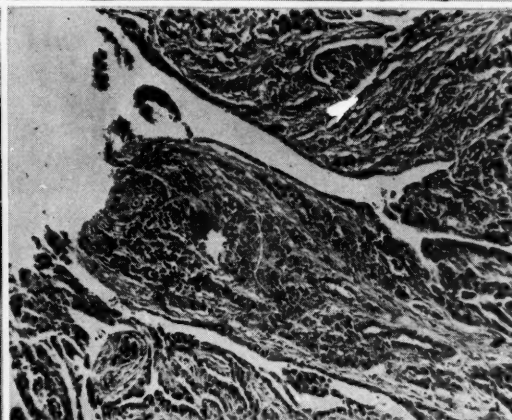


Fig. 4.

Fig. 1.—High-power view of vaginal smear. The cells are well differentiated adenocarcinoma cells.

Fig. 2.—Note the clumps of malignant cells and tumor giant cell. (High-power view of vaginal smear.)

Fig. 3.—Gross appearance of tumor of right tube found in the fimbriated end (2.3 by 0.7 by 0.5 cm.). This is shown in the upper left-hand corner.

Fig. 4.—High-power view of tumor showing large tree-like papillae composed of numerous anaplastic cells.

The right ovary measured 1.0 by 1.2 by 0.5 cm. and appeared grossly atrophic. At the time of dissection a smear was taken from the right tube and tumor surface.

The left tube measured 10 cm. in length with an average diameter of 0.6 cm. There were no gross abnormalities. The left ovary measured 1.0 by 1.2 by 0.6 cm. and appeared grossly atrophic.

There were a few small tumor nodules in the serosa of the urinary bladder. No other peritoneal tumor was present.

*Microscopic Review.—*

Sections of endometrium showed a few endometrial glands which were markedly dilated and lined by one or two layers of columnar cells. The myometrium was more densely cellular than usual. The cervix showed marked atrophic changes, as is usual in a woman of this age. The squamous epithelium was fairly low.

Sections of the fimbriated extremity of the right Fallopian tube showed papillary thickening of the epithelial mucosa with formation of excrescences composed of deeply staining cells. Springing from the wall of the fimbriated extremity were large tree-like papillae which crowded toward the center of the lumen (Fig. 4). The epithelium was anaplastic, the cells showing very little cytoplasm and a highly malignant character.

The smear from the right tube revealed numerous malignant, undifferentiated cells with a few giant nuclei.

In sections from the proximal portion of the right tube the plicae were hyperplastic. Invading tumor cells could be identified in the submucosa. A cross section of tube at the ampulla showed epithelial, submucosal, and muscular layers infiltrated by clusters of tumor cells. At one point, however, flattened but intact epithelium could still be identified.

Sections of the middle one-third of the tube, including the segment between the ampulla and the narrow isthmus portion adjacent to the uterus, revealed a narrow lumen in which tumor cells were embedded. Numerous clusters of similar tumor cells were evident in the thick muscular layers.

In sections extending through the isthmus to the interstitial portion and including the cornu, the lumen was extremely narrow and dense fibrous tissue and muscular elements surrounded it. The epithelium was flattened and atrophic. However, numerous neoplastic cells could be identified apparently arising from the lining epithelial cells. Throughout the interlacing meshwork of muscular and fibrous tissues, numerous clusters of tumor cells were also evident.

Sections of peritoneal implants from the serosa of the urinary bladder showed a structure resembling that of the primary tumor with papillary excrescences covered by columnar epithelium of many layers' thickness.

Sections of the ovary showed large corpora albicantia and numerous sclerotic arteries. A few carcinoma cells could be identified in the peripheral portion of the right ovary.

**Comment and Summary**

Well-preserved tumor cells may be desquamated from the surface of the ovary in the case of ovarian carcinoma or from the tubal mucosa in primary carcinoma of the uterine tube. These cells may be carried through the lumen of the tube by peristalsis or ciliary movement, or both, and then through the uterine canal to appear in vaginal secretions.

In the case described malignant tumor cells were identified in the stained smears of vaginal secretions which were examined as a routine procedure at necropsy. Complete examination revealed a primary adenocarcinoma of the right fimbriated extremity of the Fallopian tube. This diagnosis had not been suspected during life. There was no evidence of tumor in the endometrium nor in the cervix.

The appearance of tumor cells in vaginal smears in extrauterine carcinomas is rare. Papanicolaou<sup>13, 14</sup> mentioned cases in which the smears showed numerous compact or oval cells when the atrophy was pronounced. The appearance of these large, oval, more basal cells in the smears resulted from a thinning of the epithelium with the absence of a well-developed super-



ficial zone. The presence of such cells, however, without evidence of primary tumor in the cervix or endometrium is strongly suggestive of a primary site in the uterine tube or ovary. In these cases careful and complete investigation of the entire generative tract is mandatory.

I wish to express my deep appreciation to Dr. Helen R. Prieto, who has offered many valuable suggestions.

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## THE DIAGNOSIS AND PROGNOSIS OF FEMALE GENITAL TUBERCULOSIS

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GENITAL tuberculosis is a more localized manifestation of a systemic disease, the primary focus of which is usually in the chest or gastrointestinal tract. Accordingly, in women the world over, the frequency of tuberculous infections of the reproductive organs ranks third; the lungs and gastrointestinal tract and peritoneum being more often involved.

Until fairly recently, this form of female tuberculosis has been considered rare or uncommon, difficult to diagnose, and—above all—lacking adequate therapy. Wharton<sup>1</sup> has stated that genital tuberculosis is one of the most interesting gynecological problems and one of the most difficult to diagnose, because of the manner in which it masquerades as other gynecological conditions. Our experience at the Cook County Hospital is in full accord with this impression, but we do not believe that genital tuberculosis is a rare or uncommon disease. It is generally agreed that 5 per cent or less of all disease of the Fallopian tube is due to tuberculosis. It has also been variously reported that from 1.0<sup>2, 3</sup> to 6.0 per cent<sup>4, 5</sup> of all sterility problems are due to tuberculosis. The failure to recognize and appreciate the extremely variable signs and symptoms which the patient presents to her doctor has been one of our greatest diagnostic shortcomings.

Since January, 1948, we have made a particular study of 64 patients with genitoperitoneal tuberculosis. Fifty-two patients were operated upon, and 12 were not. Of the surgical group, 36 cases were correctly diagnosed before surgery, while 16 were misdiagnosed and initially operated upon for other conditions than genital tuberculosis. Eleven of this latter group were subsequently reoperated upon, after a course of drug therapy. These 16 patients were all seen and examined by interns, residents, associates, and attending physicians who are on the alert for this disease. Accordingly, the purpose of this paper is twofold: first, to help reduce the frequency of genital tuberculosis discovered incidentally to laparotomy or curettage, second, to relate some of our experiences in the diagnosis and treatment of this disease process, during the past four and one-half years.

\*Presented at the six hundred thirty-ninth regular meeting of the Chicago Gynecological Society, April 16, 1954.

### Diagnosis of Female Genital Tuberculosis

Patients were referred to us from the departments of medicine, general surgery, other gynecological services, and from the tuberculosis service. On our service, they had the benefit of a repeated physical examination and laboratory studies, in order to get the added advice of an internist on the general picture of tuberculosis. Eight patients transferred to us from the department of general surgery had been operated upon with a mistaken diagnosis. They were referred to us because of our particular interest in the subject. Eight other patients transferred from other gynecological services were also initially operated upon with a diagnosis other than genital tuberculosis. We do not wish to imply that only these 16 patients were transferred to our service, since many others with correct diagnoses were likewise referred.

Genitoperitoneal tuberculosis has no constant symptomatology. The patients' complaints depend on: the degree of involvement, the stage of the disease process, the extent of previous surgical and/or medical therapy, and on the presence of extrapelvic lesions. The onset may be relatively acute or insidious. In order of frequency we noted: (1) weight loss and fatigue, (2) menstrual disturbances, wherein metromenorrhagia prevails, and amenorrhea is least common, (3) abdominopelvic distress, (4) abdominal distention, (5) chills and fever, (6) leukorrhea, (7) nausea and vomiting, (8) sterility, (9) coughing, (10) diarrhea, and (11) dyspareunia. Cervical lesions were characterized by the presence of leukorrhea and/or vaginal bleeding. Patients so afflicted complained of pain only when there was noted co-existent pathology above the level of the cervix.

#### 1. *Clinical Picture.*—

The clinical picture presented by the patient depended on four factors: (1) whether the disease was in the acute, subacute, or chronic stage; (2) the type and extent of the infection; (3) presence of the primary focus; and (4) exacerbation of a previously existing lesion. In some patients the course was mild and there was noted little or no incapacitation. Physical findings as a rule were suggestive of a chronic pelvic inflammatory disease rather than genital tuberculosis.

More typical of the County Hospital patients were those who suffered progressive attacks, and were admitted in moderately or far advanced stages. In this group the generalized complaints were more marked. Physical examinations usually revealed: a distended abdomen, with or without palpable doughiness; the presence of ascites; pelvic and/or abdominal masses; the uterus and adnexa seldom discrete, more often a part of an inadequately outlined pelvic mass that often extended into the abdomen; the cervix showing either minimal findings, or altered by erosions, ulcerations, or granulations; the vagina reddened, and containing a yellow mucopurulent discharge; with the labia most frequently displaying no changes.

#### 2. *Roentgenologic Studies.*—

Routine chest and gastrointestinal studies were made on all patients. Those who had been subjected to exploratory laparotomies while on other services received their x-ray studies during their subsequent convalescence.

*A. Chest:* Twenty-five patients showed evidence of pulmonary involvement. Eleven presented a picture of acute infection, of whom 2 had bilateral lesions, one or more cavities, and positive sputa. Seven patients had pleurisy with effusion, and aspirations were performed on them on one or more occasions. In only one instance was the fluid found to be positive for acid-fast organisms on culture and guinea pig inoculation. Two patients had had a unilateral thoracoplasty, with an uninvolved contralateral lung. Three patients had fibrotic changes, with or without calcifications at the apex. One patient had pulmonary

edema associated with a decompensated heart. Her tuberculous lesion, located in the cervix, was noted during the course of a routine physical examination. One patient showed bilateral apical calcifications.

Sixteen of these 25 patients had lesions on the left side of the chest, 4 had the lesion on the right side, while 5 showed bilateral involvement.

It should be indicated that only 5 patients gave evidence of preceding pulmonary disease, e.g., one or more years prior to admission. This is in accordance with the findings of Sutherland and Garrey<sup>17</sup> in whose twenty-year study of 369 cases of genital tuberculosis only 7 patients gave previous evidence of pulmonary tuberculosis.

**B. Gastrointestinal:** Seven patients showed evidence suggesting possible or probable tuberculous involvement; one a narrowing of the rectal ampulla (she did have lymphogranuloma inguinale); one a diverticulosis of the sigmoid; one evidence of neuromuscular dysfunction; and one showed "distended small loop of bowel which is probably a sentinel ileus, secondary to the presence of ascites."

There were, of course, numerous instances where the patients had negative roentgenologic findings but at surgery the serosa was found to be studded with tubercles and/or adhesions.

### 3. Biopsies.—

Endometrial and cervical biopsies are most useful procedures. Every patient in this series had endometrial biopsies performed routinely, and in some cases, repeatedly. Tissues removed were sent to the surgical pathologist for microscopic study, and in most instances to the bacteriologist for culture and/or guinea pig inoculation. Once therapy has been started, there is no need to fear a miliary spread of the tuberculous process. Similar opinions have been stressed by Haines<sup>7</sup> and Schockaert.<sup>18</sup> It must be remembered that recovery of endometrial tissue containing the lesion is not always possible, since the infection may be focal in distribution. It is thus advisable that tissue be obtained from each surface of the uterine cavity *with emphasis on the cornu*. Several sections must be studied in order to obtain maximum results.

There has been much discussion as to when the biopsy should be taken with regard to the menstrual period. If the patient has a definite cycle, the greatest amount of tissue yielding the best possible results should be obtained several days before the bleeding phase. If there is amenorrhea or metromenorrhagia, then the biopsy can be taken any time. Ideally, a curettage is more suited for detailed study than the suction curette. Most of our specimens were obtained by use of the Randell curette. If bacteriological as well as microscopic information is desired, then one segment of tissue can be expressed into a sterile test tube and sent to the bacteriologist, while a second or third segment of tissue can be expelled into a bottle of formalin for the pathologist. The specimen referred to the bacteriologist should be kept in a cold atmosphere unless immediate study can be undertaken. Heat will desiccate the tissue and destroy organisms.

In this series of 64 patients, we noted 34 positive biopsies, of which 29 were endometrial and 5 were cervical. (Four other cases of tuberculous cervicitis were detected during the microscopic study of abdominally extirpated genitals.) Of 16 patients initially operated upon without a preoperative diagnosis of genital tuberculosis: (a) 6 patients had no preoperative biopsy reports, indicating that tuberculosis was not considered; and (b) of the remaining 12, whose abdomens were promptly closed once tuberculosis was discovered, only 4 yielded endometrial tissue positive for tuberculosis as obtained by curettage subsequent to the initial laparotomy. Of this same group of 16 patients, 11 were reoperated upon after an intensive course of drug therapy. All yielded evidence of genitoperitoneal tuberculosis, both grossly and microscopically.



#### 4. *Bacteriology.*—

Cultures and smears have only recently been used by us. Thus far the results are uniformly disappointing. One may use vaginal and uterine discharge which accumulates in the posterior cul-de-sac, or collect and culture menstrual blood. The advantage of these procedures is that they may be used repeatedly and safely. Only occasionally have we used menstrual flow for culture, though in 40 instances vaginal and/or uterine contents have been studied by culture methods.

Halbrecht<sup>6</sup> has used daily menstrual flow and cultured it on Petraghani media. By this method he has claimed to discover latent tuberculosis in a patient who had negative endometrial biopsies, and also confirmed other cases in which the endometrial biopsies were positive. Haines<sup>7</sup> stated that this procedure is not universally applicable and preferred to culture the endometrium on slants of Dorset's egg and Löwenstein-Jensen media. Others<sup>8</sup> feel that the results of culture generally are not encouraging but should be undertaken in every case. We are of the opinion that cultures of menstrual and/or intermenstrual discharges should be used in conjunction with and not stressed as a replacement for endometrial biopsies. Both procedures have their advantages and disadvantages.

In this series, culture studies (modified petraghani media) on 40 patients known to have genitoperitoneal tuberculosis, have disclosed only 7 positive results. In 15 patients, culture studies were made on tissue excised at surgery and known to be tuberculous. Only 5 positive results were obtained.

There has been but a single positive result in our study of 40 vaginal smears. Haines, who feels likewise disappointed in the smear technique, has stated that "Ziehl-Neelsen techniques entail much tedious bench work and give inferior results."<sup>7, a</sup> The answer to this objection may have been recently found. Tubercle bacilli which have been stained with carbol auramine fluoresce when the smear is illuminated with ultraviolet light. Our laboratories have not as yet utilized this procedure.

From the previous discussions one may conclude that the outcome of any bacteriological study is dependent on a number of pertinent factors: (1) the type of organisms encountered, (2) whether the organisms have been exposed to drug therapy, (3) the number of organisms in the medium, (4) laboratory technique, and (5) the type of medium.

It is also quite apparent that there is no absolute diagnostic procedure. There will be instances when the biopsies are positive microscopically, but the smears and cultures are negative. At other times the cultures will be positive while the smears and biopsies are persistently negative. Further, we have operated on 3 patients whose clinical picture suggested tuberculosis, in whom biopsy, smear, and cultures were negative, and tuberculosis definitely was proved surgically and pathologically.

We can thereby only repeat that each method of diagnosis has its weak points and its more favorable aspects. All methods should be used to complement each other.

#### 5. *Mantoux Reaction.*—

A 1:10,000 dilution of old tuberculin was used in performing the Mantoux test. If negative results were noted, a second attempt was made, using a 1:1,000 dilution. The results were positive in all patients. The most noteworthy reaction occurred in a patient subsequently proved *not* to have genital tuberculosis. Our findings thus tend to reaffirm what others have previously indicated, namely, that with different tuberculin tests, results have not proved to be specific or conclusive.<sup>9</sup>

#### 6. Hematological Studies.—

In this series, most of the patients entered with a leukocyte count that was within normal limits (6,000 to 9,000). It is not unusual, however, to encounter patients with counts of less than 6,000. Unless complicated by the presence of a mixed infection (wherein the count may rise to 10,000 or more) patients with genital tuberculosis will invariably have a relative or actual leukopenia, for most of them had a fever at the time of admission. These findings are in accord with those of Greenhill.<sup>19</sup> Therefore, the old teaching that a leukopenia indicates a grave prognosis is no longer tenable. The differential will nearly always reveal a lymphocytosis.

It is interesting to note that occasionally patients will enter the hospital with mixed infection, and the leukocyte count will show a mild to moderate leukocytosis. As the secondary infection subsides and the tubercular process predominates, the blood picture will revert to the characteristic relative or absolute leukopenia. The latter in turn shifts toward the normal leukocytic count as the acid-fast infection subsides.

Studies of the hemoglobin levels and the red cell count showed that at least 50 per cent of the patients with active infections have abnormally low figures. In the latent or silent lesions the values will obviously be close to or within normal limits.

#### 7. Sedimentation Rate.—

Sedimentation studies were seldom used because we felt that other clinical procedures are more diagnostic and significant.

#### 8. Culdoscopy and Laparoscopy.—

The usefulness of these methods was considered to be limited because of the risk associated with them. None of our patients were subjected to either procedure.

#### 9. Response to Streptomycin.—

In a woman with evidence of pelvic inflammatory disease which did not respond to bed rest, antipyretic drugs, and the usual antibiotic and chemotherapeutic agents, but reacted favorably to streptomycin (with or without para-aminosalicylic acid and isonicotinic hydrazide), we immediately suspected tuberculosis. This might be considered diagnosis by inference, but occurred often enough to be kept in mind.

#### 10. Paracentesis and Colpocentesis.—

Thirty-eight out of 64 patients had abdominal distention with minimal, moderate, or marked ascites. Six patients were subjected to one or more paracenteses prior to the beginning of drug therapy. One patient originally suspected of having carcinoma of the ovary had six punctures before streptomycin and PAS were started. It is interesting to note that none of the fluid removed from these 38 patients was found to have evidence of tuberculosis on culture or guinea pig inoculation. As a further diagnostic aid, Adair<sup>9, 10</sup> suggests that more pus cells are found in the fluid from cases of tuberculosis than of malignancy.

Two patients had colpocentesis done. One specimen was positive for tuberculosis on culture. Histological studies of the endometrium of this same patient, as well as bacteriological studies of the vaginal discharge, were negative for tuberculosis.

#### 11. Hysterosalpingography.—

The merit of this relatively new procedure has already created considerable discussion, both pro and con. At first opposition arose to the use of oil as a contrast medium.<sup>8, 10</sup> It was pointed out that Lipiodal remains in situ for a long time and is broken down into irritating substances. Flare-ups have been

seen in both tuberculous and nonspecific salpingitis after Lipiodal injections.<sup>11</sup> The use of water-soluble media, however, has obviated these complications.

Our experience with 8 patients who had hysterosalpingograms has not been remarkable. We have thus far noted only two factors: (a) that the oviducts are occluded or patent, and (b) some oviducts are tortuous, whether occluded or patent. At present, our group is of the opinion that hysterosalpingography is a useful method for aiding in the diagnosis of chronic tuberculous salpingitis but less reliable for tuberculous endometritis. It should be used in all suspected cases of genital tuberculosis unless an acute salpingitis is present, and should be complemented by the accepted bacteriological and histological studies of endometrial tissue.

### Prognosis of Female Genital Tuberculosis

The recent advent of chemotherapeutic and antibiotic drugs which are antituberculosis in behavior, has presented new horizons of hope for this chronic, destructive, and pertinacious disease. Perusal of the literature even up to 1950 showed a distressingly gloomy future for many patients afflicted with genital tuberculosis.

In August, 1949, a study was made by us of 28 patients with gynecological tuberculosis at the Cook County Hospital, covering the three-year interval of 1945 to 1947, inclusive.

TABLE I. TREATMENT, 1945-1947

	DIED	ALIVE	MISSING	TOTAL
Surgery	2	3	1	6
Conservative with paracentesis	5	0	3	8
Conservative alone	11	1	2	14
Total	18	4	6	28

These patients had been treated by the accepted procedures of the day, namely, conservative measures with and without paracentesis, pneumoperitoneum, heliotherapy, various degrees of surgery, and with the sulfonamide-penicillin group. House-to-house investigation proved that 18 were deceased, 4 were alive, and 6 could not be located. Eleven of the 18 who died were from the nonsurgically treated group.

The introduction of streptomycin was a milestone in our efforts to arrest or cure genital tuberculosis. The combination of the streptomycin group with para-aminosalicylic acid (PAS) and/or isonicotinic acid hydrazide (INH) has dramatically changed the usual chain of events regarding patient response and prognosis for the future. Silent lesions in the endometrium and/or oviducts respond promptly to these drugs. The regression and healing of the disease process has been repeatedly followed by bacteriological, microscopic, and roentgenological studies. Pregnancies are now known to have occurred following drug therapy provided the oviduct had not been occluded, distorted, or the mucosa too extensively involved.

More advanced pelvic lesions still require prolonged and diligent supervision. Many patients heretofore considered candidates for surgery have been spared the ordeal and its possible associated complications because of early diagnosis and response to the presently available drugs. We have long since learned, however, that in many instances subsequent surgical intervention is still necessary. This is particularly true of those patients who present adnexal masses, abscesses, prominent thickenings and infiltrations, and ascites. In these cases, streptomycin, PAS, and/or INH have reduced operative and postoperative hazards.



The outlook is even more optimistic since present experiments indicate that radioactive isoniazid is freely diffusible into dense caseous lesions.<sup>12</sup> Thus the answer to one of the most vital and practical considerations in the therapy of tuberculosis is probably close to solution. At long last we are beginning to encroach upon the tubercle bacillus, heretofore safely guarded in necrotic, caseous lesions, beyond the reach of available antibiotics and chemotherapeutic agents.

The prognosis for tuberculosis of the cervix, whether the lesion apparently is limited to the cervix per se, or is in association with foci at higher levels, has also undergone auspicious changes. Our experience with 10 cases had left us with the following impressions: (a) if complete investigation indicates that the disease is apparently limited to the cervix, and if the adnexa are free or only minimally involved after *adequate combined drug therapy*, these patients will usually do well and not need surgery; (b) if the appearance of the cervix is restored to normal but the associated pelvic lesions remain prominent, then surgery will have to be performed.

Although we have not seen a single case of tuberculosis of the vulva or vagina in four and one-half years, the literature indicates that this rare lesion, if localized and unassociated with the usual miliary tuberculosis, can be healed or cured with the proper use of present-day drugs, complemented when necessary by surgery. The most prompt and outstanding response of any acid-fast lesion to antituberculosis drugs is found in the superficial lesions of the skin, vulva, and vagina. Dermatologists and gynecologists alike have shared this experience with enthusiasm.<sup>13-16</sup>

In conclusion, it thus seems that the present-day prognosis of genito-peritoneal tuberculosis depends on one or more of the following factors: (1) location of the lesion or lesions; (2) pathological type, and extent of the lesion; (3) bacterial virulence and its sensitivity or resistance to drug therapy; (4) the patient's inherent resistance, and ability to rally under the influence of drug therapy; (5) response of the lesion to drug therapy and rest; (6) diffusibility of the drugs in necrotic, caseous, and abscessed lesions; (7) surgical amenability of persistent lesions; (8) recurrences either at the original or distal sites, and their response to further therapy.

### Summary and Conclusions

1. Genital tuberculosis, silent or active, may be one of the most difficult gynecological diagnoses to make because of the manner in which it masquerades as other gynecological conditions. The incidence of missed preoperative diagnosis (30 per cent) attests this opinion.

2. The most common conditions mistaken for genital tuberculosis were: (a) partial or complete intestinal obstruction; (b) chronic pelvic inflammatory disease; (c) recurrent appendicitis; and (d) fibromyomas of the uterus with pelvic inflammatory disease.

3. Routine chest and gastrointestinal studies should be made on all patients, whether they have been operated upon or not. In this series, 25 patients (27.5 per cent) gave evidence of pulmonary involvement. Ten patients (6.4 per cent) showed evidences of gastrointestinal abnormalities, of which 7 were suggestive of tuberculous involvement.

4. Endometrial and cervical histological biopsies are most useful procedures. These methods do not compete with bacteriological studies but are complementary.



5. Hematological studies show two important features: (a) a relative or absolute leukopenia will be noted in most cases of genital tuberculosis; (b) at least 50 per cent of patients with active infections will have abnormally low hemoglobin levels.

6. The discouragingly low incidence of positive smears by the Ziehl-Neelsen technique indicates the desirability of exploring further the fluorescing auramine technique.

7. A follow-up study of 28 patients with female genital tuberculosis as treated with accepted procedures of the day (1945 to 1947, inclusive) disclosed that within two years after leaving the hospital 18 were dead, 4 were alive, and 6 were missing. It is not unfair to assume that one or more of the latter must have also died.

8. The combination of streptomycin with PAS or INH has dramatically changed not only the course of the disease, but the treatment and prognosis as well.

9. As can be expected from the behavior of such a chronic disease, more advanced pelvic lesions still require prolonged therapy and some form of excisional surgery. On the other hand, many patients heretofore considered candidates for surgery have been spared the ordeal.

10. The serious complications of recurrences or relapses had been encountered in 3 patients *prior* to the use of combined therapy (37 patients), and in but one patient *since* the use of combined therapy (27 patients). In the follow-up clinic such possibilities are constantly kept in mind. In our previous reports it was indicated that, with the use of streptomycin or dihydrostreptomycin alone, relapses occasionally did not respond to further therapy (2 such patients died). The recent addition of PAS and INH has lessened that possibility but by no means has it been eliminated.

11. A listing of those criteria which apparently determine the prognosis of female genital tuberculosis is offered for consideration.

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### Discussion

DR. AARON E. KANTER.—The essayists have shown that a diagnosis of genital tuberculosis is no easy matter and many steps must be taken in some instances to prove the presence of tuberculosis. The disease, both clinically and grossly, resembles other pelvic pathological conditions so closely that various methods must be used to make a diagnosis. In many cases of long standing there is a mixed infection which masks the particular characteristics of tuberculosis. Without the added diagnostic methods, tuberculosis of the genitals is made only in a virgin with pelvic pathology with no history of an acute infection, or in a patient whose symptoms came on very insidiously.

It is my belief that the routine postcolpopuncture for obtaining material from the posterior cul-de-sac for culture and guinea pig inoculation will increase our percentage of diagnoses.

In a patient with pelvic disease who does not improve under the usual antibiotics and chemotherapeutic agents but does improve under streptomycin, one should think strongly of tuberculosis.

In general, one must be tuberculosis conscious to have a better batting average to make such a diagnosis, just as one who is ectopic minded will make more frequent diagnoses of extrauterine pregnancy. If more biopsies of the cervix and ovary are taken when tuberculosis is discovered, there will be found a much greater percentage of tuberculosis in these organs.

An institution like the County Hospital with its predominantly Negro population will show a greater incidence of genital tuberculosis than our private practice. In fact, in my experience, tuberculosis was discovered most often in the workup for sterility where a biopsy of the endometrium disclosed this lesion.

The question as to what method of treatment is best in cases of genital tuberculosis in women has been a matter of much discussion in the past two decades. Some authorities, especially the English and American workers, have recommended radical surgery. Others again have given conservative treatment a trial and resorted to surgery only in those cases in which this treatment proved unsuccessful.

The essayists and other workers have shown that streptomycin, PAS, and INH are very effective in tuberculosis of the female genitals, and in many instances the disease disappears, circumventing surgery entirely. The use of these drugs lowers the incidence of complications, lessens the operative risk, and facilitates a radical operation technically. In cases where tuberculosis was not diagnosed and where at initial surgery technical difficulties prevented completing the operation, after a course of streptomycin PAS and INH therapy, the surgery became very simple as cleavage planes became discernible. In fact, in some cases no surgery was indicated. One must, however, continue treatment for many months after the patient is apparently cured. At least two to three years must elapse before these patients should attempt a pregnancy, for pregnancy definitely causes a rapid progress of the disease.

Although not many cases of pregnancy following conservative treatment have been reported as yet, it is my feeling that pregnancy may occur in many patients who have not had the benefit of this therapy.

One hardly realizes how much effort was expended in carrying out this work, particularly at the County Hospital. All of us on the Gynecological Staff have been aided in no small manner in seeing this work carried on. We are more alert to the diagnosis and have rendered the patients better service.

DR. J. P. GREENHILL.—Most of you know from reading the literature that throughout the world tuberculosis of the genital organs is very common. I have been interested in this subject for thirty-five years, because I had the privilege of studying 200 proved cases at Johns Hopkins Hospital. There are some countries like Scotland, Israel, and Belgium where about 5 to 7 per cent of all women who come to sterility clinics have proved tuberculosis of the pelvic organs. We have not found this frequency in our country. Some foreigners insist we overlook many cases of pelvic tuberculosis because we do not look for the disease thoroughly enough. Perhaps this is true.

Dr. Kanter made a statement about pregnancy in women who have had pelvic tuberculosis. This is very discouraging. There have been only five full-term babies born after healed pelvic tuberculosis, as reported in the world literature. Dr. Zummo said there were two in their series. •

A word about diagnosis. Halbrecht insists that his best means to prove the diagnosis is by culture of the menstrual blood. However, the results with this diagnostic aid in England are discouraging.

DR. ZUMMO (Closing).—Up until January, 1953, we used streptomycin and PAS in our treatment of those patients with genital tuberculosis. Since January, 1953, we have been using streptomycin and isoniazid. We started out using therapy in dosages recommended by the Veterans Administration. At the beginning 2 Gm. of streptomycin a week was given as 1 Gm. intramuscularly twice weekly. We also standardized our treatment with INH to 300 mg. per day. A review of our results in July, 1953, led us to the conclusion that since we were dealing usually with a diffuse hyperplastic type of lesion, more streptomycin had to be given. Accordingly, our present regimen consists of 1 Gm. of streptomycin three times a week and INH, 300 mg. per day.

## **ESTRADIOL 17-BETA-CYCLOPENTYLPROPIONATE, A LONG-ACTING ESTROGEN\***

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**I**N A previous communication by Soule and Yanow,<sup>1</sup> a preliminary study of estradiol 17-beta-cyclopentylpropionate was reported. The potential estrogenic value of this drug was established, based upon the prolonged stimulatory effect on the vaginal mucosa as measured by the percentage of cornified cells noted following administration of the drug.

The duration of action of estrogens administered parenterally has been the subject of systemic research in test animals, but only a few analogous systemic studies of the duration of action of these substances have been done in human beings. There are several ways of studying drugs of this type. Many studies have been based on clinical subjective response to medication as determined by the suppression of "hot flashes" and/or other subjective symptoms. Although the subjective response to medication by the patient is the final clinical test, its investigative value is definitely disputed. The conditions for which estrogens are administered are uniformly intimately associated with difficulty of honest evaluation. It is most difficult to separate the psychic response from the somatic factors. In clinical therapy such division is not necessary or even advisable, but in fundamental evaluation of the therapeutic efficacy of a drug, it is of utmost importance. Therefore, one may turn to objective methods of study.

The physiological activity of estrogens can be evaluated objectively by noting the latent period between the cessation of therapy and the onset of uterine bleeding. Another objective means is the evaluation of the amount and consistency of the cervical mucus. Still another way is to follow by vaginal smears the change in cornification of the cells of the vagina following drug therapy. These are truly objective methods of study. There may be no direct relationship between the end points of these studies and the subjective response in the person being studied.

The vaginal smear is a method of measuring estrogenic activity which is simple in performance, inexpensive, and readily accessible. To date this method has been applied to the assessment of estrogenic activity in human beings most extensively by Shorr<sup>2</sup> and his co-workers. This type of observation, we believe, has merit because of its objectivity and because it lends itself most readily to multiple and continuous observations.

It is well established that estradiol is the primary hormone of the ovarian follicle. It is probably produced mainly by the theca interna, although it is known to be made elsewhere in the ovary since it can be extracted from the ovarian stroma alone. The natural hormone estradiol and its derivatives are

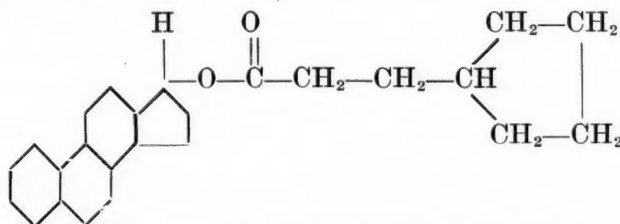
\*Presented at a meeting of the St. Louis Gynecological Society, April 8, 1954.



steroids with the basic structure  $\Delta 1,3,5$ -estratriene. They represent successive stages of reduction. Alpha estradiol represents the highest state of reduction in this series and is the most potent biologically. It is approximately twelve times as active as estrone, and sixty-six times as active as estriol. The next stage of oxidation is estrone, and finally, with the addition of one molecule of water, is estriol. These compounds can be esterified at the hydroxyl groups at positions 3 and 17; thus we get the benzoate, dipropionate, and now the cyclopentylpropionate and others. It seems likely that, in the human organism, alpha estradiol is in equilibrium with estrone and that either of these compounds may lead to the formation of estriol. This work is probably done in the liver where there is an oxidative enzyme system.<sup>3</sup>

Recently Ferin<sup>4</sup> reported an analysis of various estradiol preparations by the "estrogen withdrawal bleeding" method as well as vaginal smear and cervical mucus studies. Emphasis was placed on the former, however. He compared a number of natural and synthetic esterified estrogens: estradiol 3-benzoate, estradiol 3-furoate, diethylstilbestrol dipropionate and diacetate in oil; estradiol dipropionate in oil; estradiol 17-caprylate and estradiol 3-benzoate 17-n-butyrate in oil; diethylstilbestrol-n-dibutyrate in oil and diethylstilbestrol difuroate in small crystal oil suspension; estradiol 3-benzoate in aqueous suspension; estradiol 3-benzoate in microcrystalline aqueous suspension and diethylstilbestrol difuroate in large crystal oil suspension. The drugs were reported in the order of increasing duration of action.

Interest in estradiol 17-beta-cyclopentylpropionate\* stems from work by Lloyd and Fredericks,<sup>5</sup> Ott and his co-workers,<sup>6</sup> and McCullagh and his co-workers<sup>7</sup> which led to the acceptance of testosterone cyclopentylpropionate as a clinically valuable drug. The objective test that these men used was the 17-ketosteroid excretion study as well as subjective studies of the number of nocturnal emissions and the number of erections daily in impotent males, eunuchs, and hypogonadal men. Lloyd and Fredericks<sup>5</sup> conclude that the testosterone cyclopentylpropionate effect lasts for twenty-eight days or longer as compared with the testosterone propionate effect of fourteen days or less. McCullagh<sup>7</sup> showed that the excretion of 17-ketosteroids following the administration of testosterone cyclopentylpropionate is considerably more prolonged than that following an equal dose of testosterone propionate in oil. The return to normal with testosterone cyclopentylpropionate occurred in nine to fifteen days whereas with testosterone propionate it occurred in four to five days. Because of the enthusiasm for testosterone cyclopentylpropionate, it was deemed advisable to investigate the corresponding ester of estradiol.

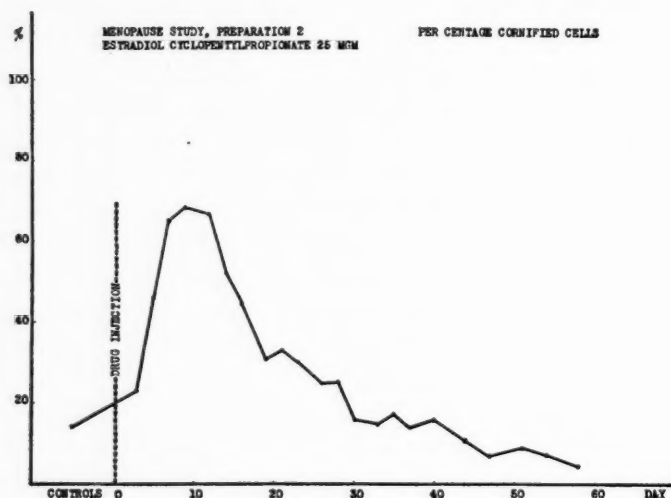


Estradiol 17-beta-cyclopentylpropionate

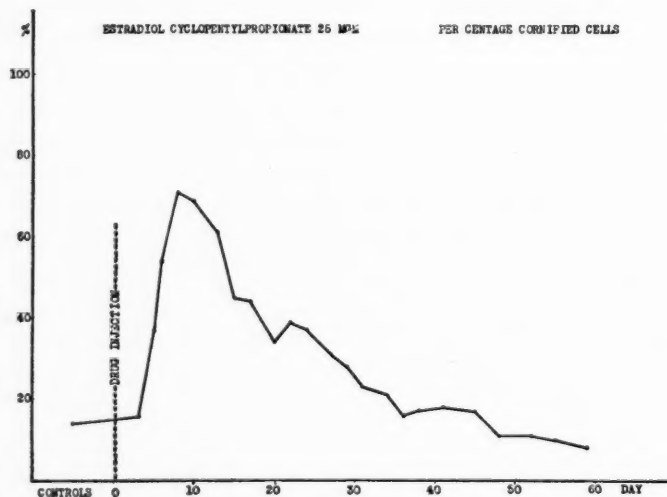
\*Supplied through the courtesy of Drs. Earl Burbidge, A. F. Hailman, and C. J. O'Donovan, The Upjohn Company.

### Material

The source of patients used for this investigation was two private nursing homes in the St. Louis area. The subjects were all women past the menopause, ranging in age from 49 to 93. Thirty-three women were used in the study. None had had a hysterectomy. Since two separate series were studied, some of the subjects were used twice. Of this number of patients only 4 were less than 60 years of age, and only 6 were less than 70. Thus the great majority



Graph 1.—This is a composite graph of the 10 patients who received "Menopause Study, Preparation 2" (estradiol cyclopentylpropionate, 25 mg.) showing the percentage of cornified vaginal epithelial cells before and after injection of the drug. Note the similarity to Graph 2.



Graph 2.—This composite graph of the 11 subjects who received estradiol cyclopentylpropionate, 25 mg., shows the percentage of cornified vaginal epithelial cells before and after injection of the drug.

were twenty years or more past the menopause. At the beginning of the study a normal female pelvis was demonstrated by vaginal examination.

In the first series two drugs were studied. One of these, labeled "Menopause Study, Preparation 2," was an unknown drug to the investigators. The other contained estradiol cyclopentylpropionate, 5 mg. per cubic centimeter. Only after the investigation was completed and comparative graphs drawn, did we learn that these medications were the same (Graphs 1 and 2). Thus 21 patients received 25 mg. of estradiol 17-beta-cyclopentylpropionate in one injection intramuscularly.

Three medications were used in the second series of patients. Twenty-five patients were divided into three groups. Nine patients received 5 mg. of estradiol dipropionate, 9 received 5 mg. of estradiol 17-beta-cyclopentylpropionate, and 7 were injected with 5 mg. estradiol benzoate. All medications were given intramuscularly. For our purposes these were numbered Groups II, III, and IV, respectively.

### Procedure

The vaginal smears were obtained by wetting a cotton applicator with normal saline, and, with the labia spread, inserting the applicator into the vagina. The applicator was rotated gently several times and then withdrawn. A smear was made immediately by wiping the cotton in a circular motion on the slide which had been previously labeled with a paper clip placed over the end to prevent other slides from adhering to it. After the smear was made, it was dropped promptly into a fixing solution consisting of equal parts of ether and 95 per cent alcohol.

After at least thirty minutes' fixation, the slides were stained in accordance with the technique outlined by Papanicolaou.<sup>8</sup>

Three or four control smears were taken before the subjects received their hormone injection. Following the injection, a slide was made every other day for the first two weeks and then twice weekly thereafter until the appearance of the smear returned to that of the control series.

Interpretation of the smears was done by locating fields where the cells could be distinguished individually. One hundred cells were counted, were classified as basal, precornified or cornified, and the percentage of each type of cell was recorded. Later graphs were made of each individual record and a final composite graph was made of all records in each group.

### Results

*First Series.*—In the group of 21 patients who received 25 mg. of estradiol 17-beta-cyclopentylpropionate, a marked and prompt rise in the number of cornified vaginal epithelial cells occurred (Graphs 1 and 2). The percentage of cells rose from a control average of fourteen to a peak of sixty-eight and seventy on days eight and nine. Actually the percentage was at a high level from the seventh to the thirteenth day, following which a precipitous fall occurred ending on day twenty. The decline then became more gradual and the percentage of cornified cells returned to the preinjection level on days thirty and thirty-six in the known and unknowns of this group, respectively.

Nine of these patients had withdrawal bleeding varying from mere spotting to heavy flow. One 86-year-old woman bled heavily for five days starting on day thirty-seven. One 83-year-old bled heavily for seven days beginning on the fifty-first day after injection. One subject, aged 86, spotted intermittently from the twenty-seventh to the thirty-ninth day. Only spotting occurred in another 83-year-old on days twenty-six and twenty-seven.

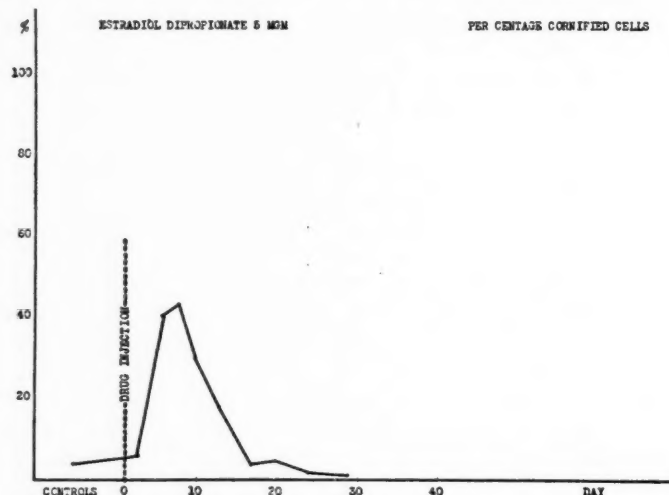
Mild bleeding occurred from days forty-six to fifty in one 56-year-old subject. Four days of heavy bleeding started on the twenty-sixth day in another

78-year-old. A 70-year-old spotted for five days starting on day forty-one. Very heavy uterine bleeding occurred for twelve days starting on day thirty-nine in another 70-year-old.

Five patients of this group complained of some enlargement and tenderness of the breasts and nipples. They complained, too, of itching of the nipple and spontaneous nipple erection. This started on the ninth day post injection and lasted approximately a week.

*Second Series.*—Groups II, III, and IV are compared.

As stated previously, the 9 patients in Group II each received 5 mg. of estradiol dipropionate parenterally (Graph 3). From a control average of 4 per cent cornified cells there was a sudden rise to 42 per cent on day eight and then a precipitous fall to the control level, reaching that level on day seventeen. Only one patient, aged 70, had withdrawal bleeding. This started on the seventeenth day following the injection and lasted eight days. This same patient had bled starting on the forty-first day after the injection of 25 mg. of estradiol 17-beta-cyclopentylpropionate. On the sixteenth day after injection, one 85-year-old blind lady had a realistic nightmare in which she thought she had been raped. We could not convince her that she was dreaming. No other subjective complaints occurred in this group.



Graph 3.—A composite graph denoting the percentage of cornified vaginal epithelial cells in the 9 patients who received 5 mg. estradiol dipropionate.

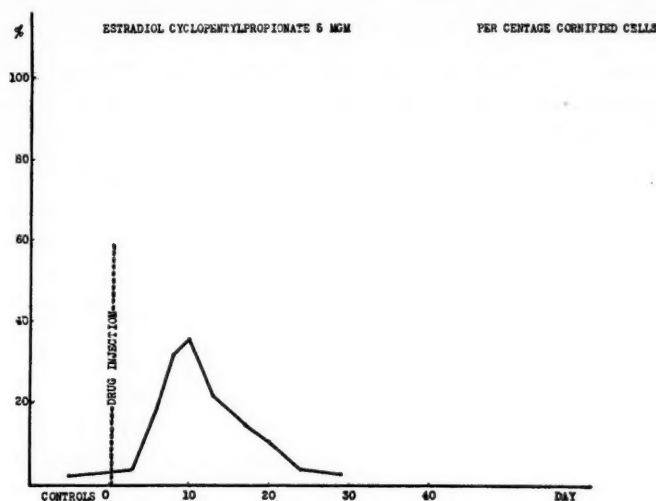
Each of the 9 patients in Group III received 5 mg. of estradiol 17-beta-cyclopentylpropionate (Graph 4). From 2 per cent cornified cells in the controls, a peak of 36 per cent was reached on day ten, following which a gradual decline was noted to the control level on day twenty-four. One 79-year-old woman had three days of spotting starting on the twenty-ninth postinjection day. No subjective response was noted by any of the 9 patients in this group.

In the group of 7 patients who received 5 mg. of estradiol benzoate, Group IV (Graph 5) only a relatively slight response was noted. A peak of 25 per cent cornified cells was reached on the sixth day after injection, beginning at a control level of 2 per cent. The curve had returned to normal on day seventeen. No withdrawal bleeding or subjective symptoms occurred.

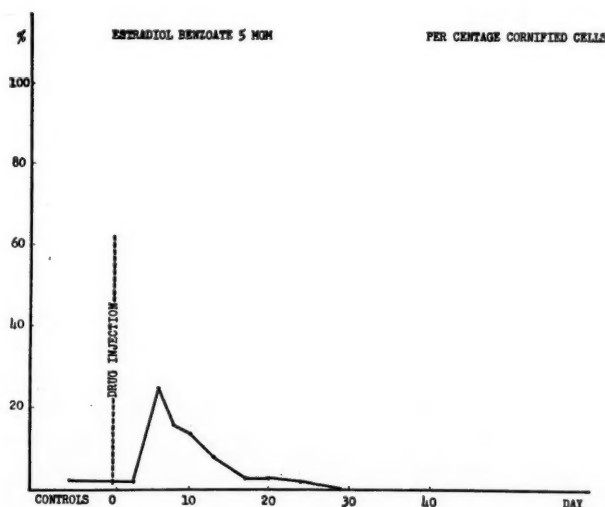
Thus with 25 mg. of estradiol 17-beta-cyclopentylpropionate, the duration of action was thirty to thirty-six days. With 5 mg. of estradiol 17-beta-cyclopentylpropionate, the duration of action was twenty-four days; with 5 mg. of estradiol dipropionate, seventeen days; and with estradiol benzoate, seventeen



days with a relatively weak response. This compared very favorably with the preliminary report of Soule and Yanow<sup>1</sup> in which they showed the duration of action of 5 mg. of estradiol 17-beta-cyclopentylpropionate to be 22.9 days, and 5 mg. of estradiol dipropionate to be 17.9 days for a ratio of 127 to 100. The present ratio is 141:100:100.



Graph 4.—A composite graph showing the percentage of cornified vaginal epithelial cells in 9 subjects who received 5 mg. estradiol cyclopentylpropionate. Note the prolonged duration of activity as compared with Graphs 3 and 5.



Graph 5.—A composite graph which shows the percentage of cornified vaginal epithelial cells in the 7 patients who received 5 mg. estradiol benzoate.

### Comment

To date estradiol benzoate and estradiol dipropionate are the most widely administered esters of estradiol. The reports of Ferin<sup>4</sup> and Vogel and her associates<sup>9, 10</sup> indicate that research, both investigative and clinical, is concerned

with other esters of this fundamental estrogen. A preliminary study of estradiol 17-beta-cyclopentylpropionate showed sufficient positive evidence of prolongation of activity to warrant further investigation.

The present report is concerned with the details of that further investigation. As compared with the standard esters of estradiol, estradiol 17-beta-cyclopentylpropionate is absorbed at a comparable if not more rapid speed and has a significantly prolonged effect. Its peak effect is also comparable to that of the other commonly used esters. Being a totally objective method of study of a single injection of drug, no significant subjective clinical response was anticipated nor obtained.

The withdrawal bleeding which we had was anticipated in view of the dosage of estradiol 17-beta-cyclopentylpropionate. The effective length of activity of this drug is once again borne out by the long latent period in those patients who bled. A subsequent communication will be concerned with the incidence of withdrawal bleeding when this estrogen was given in combination with testosterone.

### Summary and Conclusions

A clinical study of the cyclopentylpropionic acid ester of estradiol has been made using the objective vaginal smear method for comparing the several esters of estradiol.

As determined by the percentage of cornified cells of the vagina, estradiol 17-beta-cyclopentylpropionate is absorbed at approximately the same rate as conventionally used esters of estradiol.

The prolonged stimulation as determined by the time required for the percentage of cornified cells to return to the base line is significant.

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## THE CYTOLYTIC CHANGES OF THE VAGINAL EPITHELIAL CELLS AND THE LEUKORRHEA FOLLOWING ESTROGENIC THERAPY\*

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THE causes of leukorrhea are usually divided into physiologic, constitutional, pathologic, and unexplained.

It is the purpose of this paper to draw attention to a cause of leukorrhea which might have been placed under the unexplained causes of vaginal discharge. It is a highly acid leukorrhea without inflammatory reaction and it consists of normal squamous epithelial cells only with a healthy vaginal flora. It is generally considered that such a discharge is difficult to explain and difficult to control.

A discharge of this type is usually the leukorrhea following estrogenic therapy. If we discuss this type of leukorrhea which can be found shortly after the beginning of estrogenic therapy we have to exclude at first all other possibilities for this symptom.

The observation of leukorrhea following estrogenic therapy is usually made on patients who have complained of menopausal symptoms. Usually this post-therapeutic leukorrhea is not found in patients with atrophic vaginitis. On the contrary, in patients with atrophic vaginitis and with leukorrhea, the discharge disappears very often after local or parenteral estrogen administration. But patients with an atrophic menopausal type are generally free of menopausal symptoms.<sup>8</sup>

It is necessary to check therefore the pretherapeutic smear types. This control is relatively easy in a clinical diagnostic system where vaginal smears are made routinely from every patient before and while under treatment.

The usual cytologic findings we have seen in patients suffering from the menopausal syndrome are shown in the first two photomicrographs (Figs. 1 and 2). In nearly all cases superficial noncornified or intermediate squamous epithelial cells, which are mostly crowded and folded, are found.

The bacteriologic classification from the interpretation of the smears is never as correct as a bacterial culture is, but we can differentiate with relative ease and accuracy these six types of smears: (1) vaginal smears with mainly *Bacillus vaginalis* Döderlein, (2) vaginal smears with mixed flora, (3) vaginal smears with mainly cocci (Fig. 2), (4) vaginal smears with *Trichomonas vaginalis* (Fig. 3), (5) vaginal smears with fungi (e.g., *Leptothrix vaginalis*) (Fig. 3), and (6) vaginal smears without visible bacteria.

\*Supported by the Goldblatt Cancer Research Fund and by an Institutional Grant of the American Cancer Society.

Fig. 1.

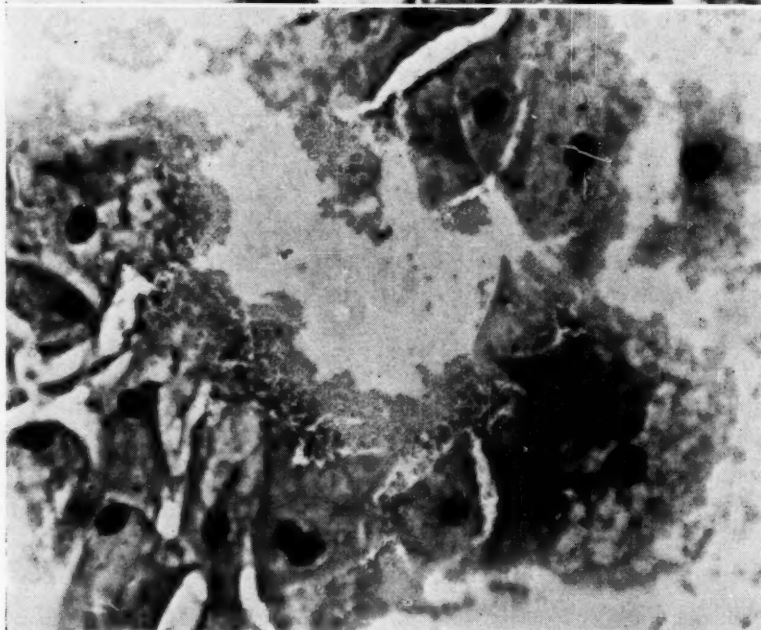
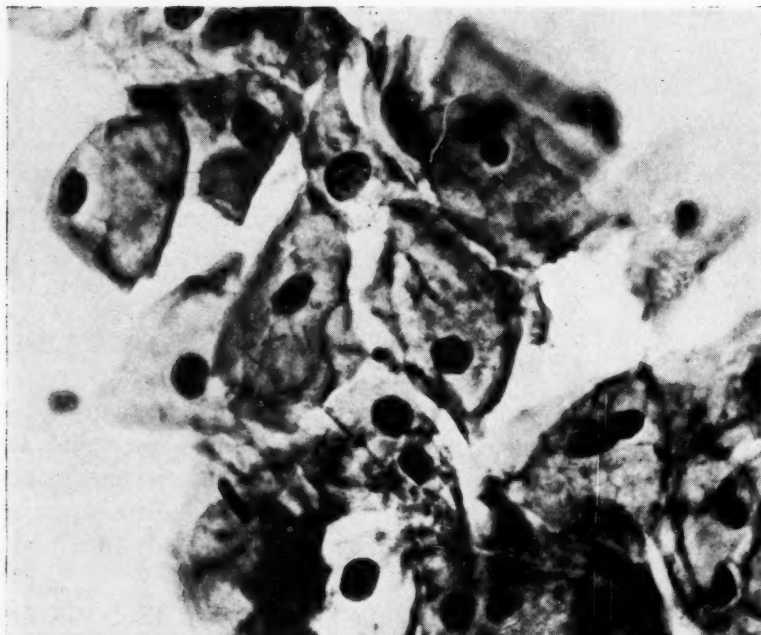


Fig. 2.

Fig. 1.—Vaginal smear of a 58-year-old patient with a severe menopausal syndrome, sixteen years after hysterectomy with bilateral salpingo-oophorectomy. The photomicrograph shows mostly intermediate and noncornified superficial squamous epithelial cells which are crowded and folded. The cells are relatively isocytotic and isonucleotic. The vaginal flora consisted in this case of few Döderlein bacilli; there was no inflammatory reaction.

Fig. 2.—Vaginal smear of a 60-year-old patient with severe menopausal symptoms twelve years after surgical castration. The photomicrograph shows intermediate and superficial noncornified squamous epithelial cells surrounded by a wall of cocci. No inflammatory reaction. The vaginal pH was 5.8. The patient did not suffer from leukorrhea.



In the first group (mainly *Bacillus vaginalis*) there are two different cytologic types: (a) vaginal smears without cytolysis and (b) vaginal smears with cytolysis (Fig. 4).

Cytolysis of this kind (Fig. 4) is due to *B. vaginalis*. We were able to show this fact experimentally.<sup>10</sup> The cytolysis due to *B. vaginalis* is a peptolysis. It can be so strong that almost no uncytolyzed cells are found in the smears (Fig. 5). The nuclei "survive" the cytoplasmic destruction for a while. We therefore find an abundant amount of free nuclei in the cellular debris and Döderlein bacilli. The bacterial cytolysis is bound to distinct cellular types. The cornified superficial cells (pyknotic nuclei, acidophilic cytoplasm) are resistant to the cytolytogenic effect of the *B. vaginalis* (Fig. 6), and the smears which contain predominantly parabasal cells (atrophic menopausal type, Fig. 7) are usually free of Döderlein bacilli. Therefore, the bacterial cytolysis can be seen only in smear types in which the cellular proliferation *does not* go up to the complete cornification and in which the stimulation is on the other hand strong enough to proliferate the epithelium at least to the intermediate cell layers.<sup>9</sup>

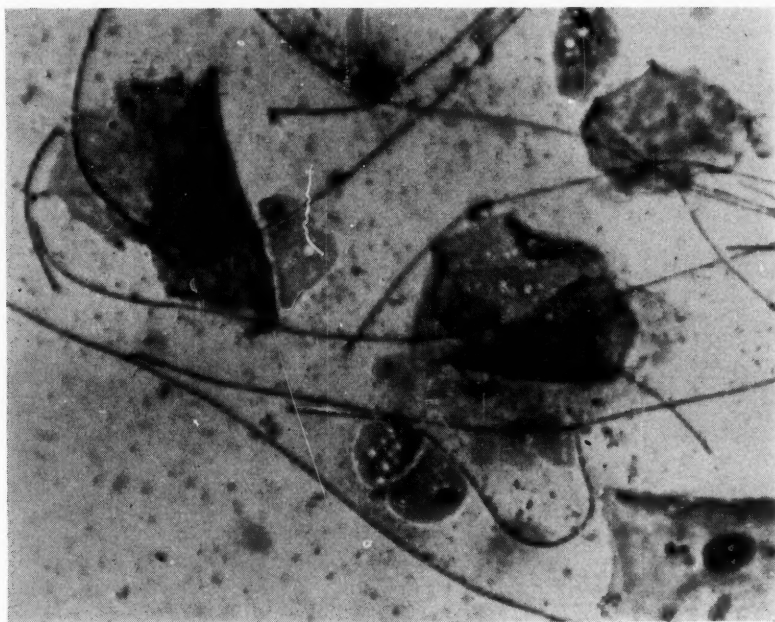


Fig. 3.—Vaginal smear of a patient with abundant *Leptothrix vaginalis*, *Trichomonas vaginalis*, and cocci.

With this description we have remaining distinct groups for diagnosis in which the cellular proliferation is present (not atrophic types), but not strong enough to produce cornification. This would exclude a strong estrogenic effect.

Which hormonal situations would be left for the bacterial cytolysis after this description? All proliferative stages in which we find the proper conditions for the growth of the Döderlein bacilli and no marked cornification of the cells: (a) pregnancy, (b) luteal phase of the menstrual cycle, (c) postmenopausal, climacteric patients, (d) premenarchal cases, (e) after treatment

Fig. 4.

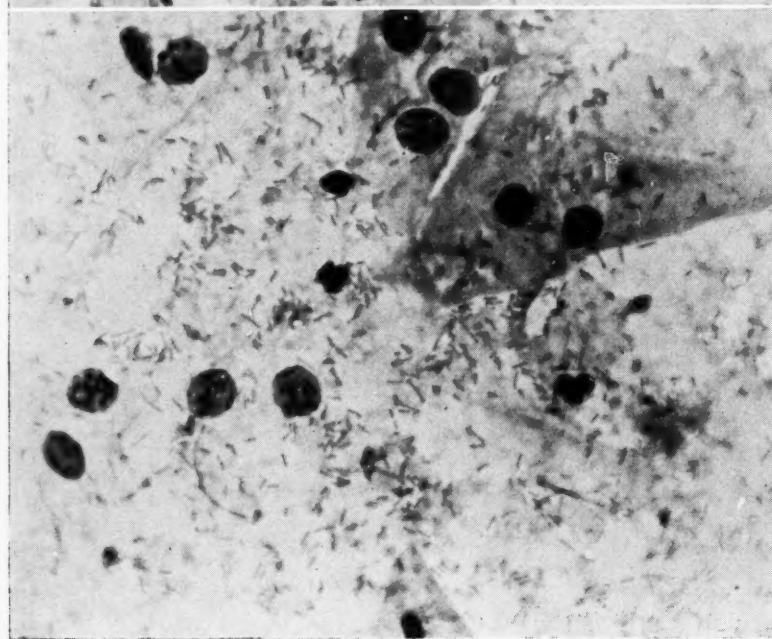
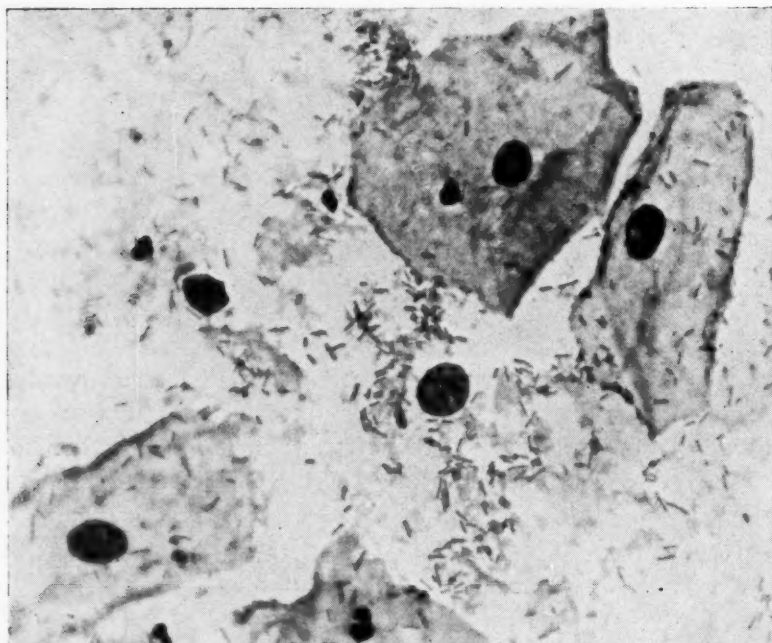


Fig. 5.

Fig. 4.—Vaginal smear of a patient in the luteal phase of the menstrual cycle. The photomicrograph shows some superficial noncornified cells, cellular debris, free nuclei, and abundant *Bacillus vaginalis*.

Fig. 5.—Vaginal smear of the same patient shown in Fig. 1, seventy-two hours after injection of 10 mg. estradiol benzoate. The photomicrograph shows few noncornified cells and many free nuclei of cytolyzed cells and abundant *Bacillus vaginalis*. The patient complained of increased leukorrhea.

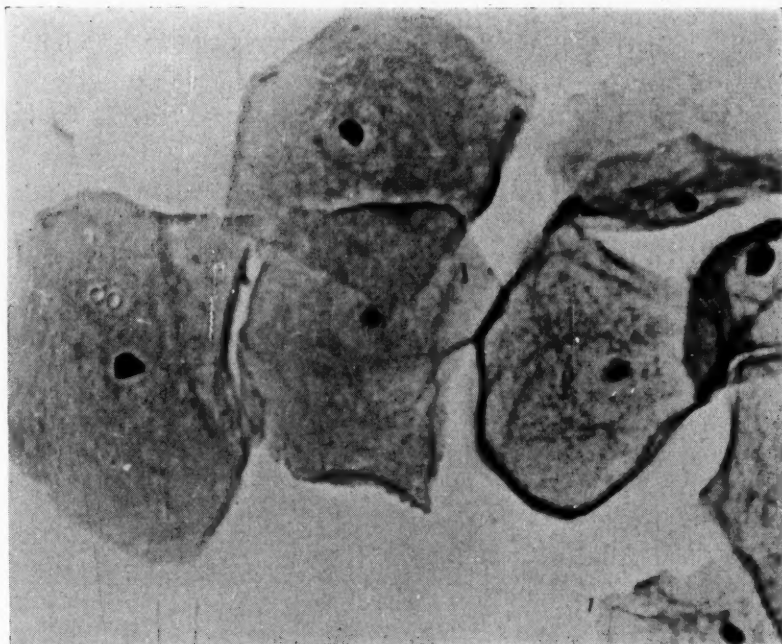


Fig. 6.—Vaginal smear of the same patient shown in Fig. 4, in the late follicular phase of the cycle. The photomicrograph shows superficial cornified cells and few Döderlein bacilli. Cornified cells are resistant to the cytolytic effect of the *Bacillus vaginalis*.

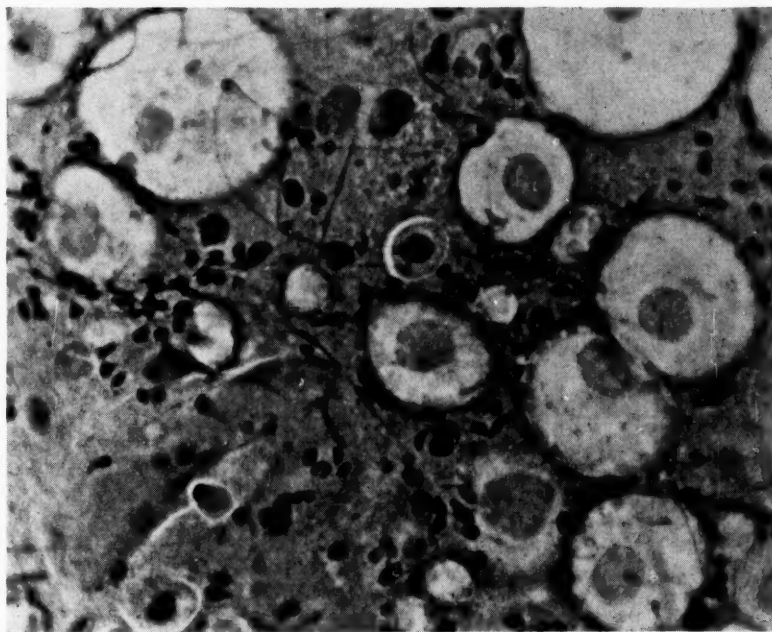


Fig. 7.—Vaginal smear of a senile patient. The photomicrograph shows mostly anisocytotic and anisonucleotic parabasal cells and degenerated leukocytes. The vaginal flora consisted mainly of cocci. Patients showing this atrophic menopausal type are usually free of menopausal syndrome.

with androgens, with mixtures of androgens and estrogens, with mixtures of androgens and progesterone, with progesterone or with mixtures of progesterone and estrogens.

We see that the cytolytic changes *are not* due to a *specific* hormonal situation but are bound to a specific cellular layer which can occur for different hormonal reasons.

To return to the previous question of leukorrhea following estrogenic therapy, we have now established that the patients with the climacteric syndrome have usually a proliferative-cell type which is affective to the cytolytogenic effect of the *B. vaginalis* Döderlein.

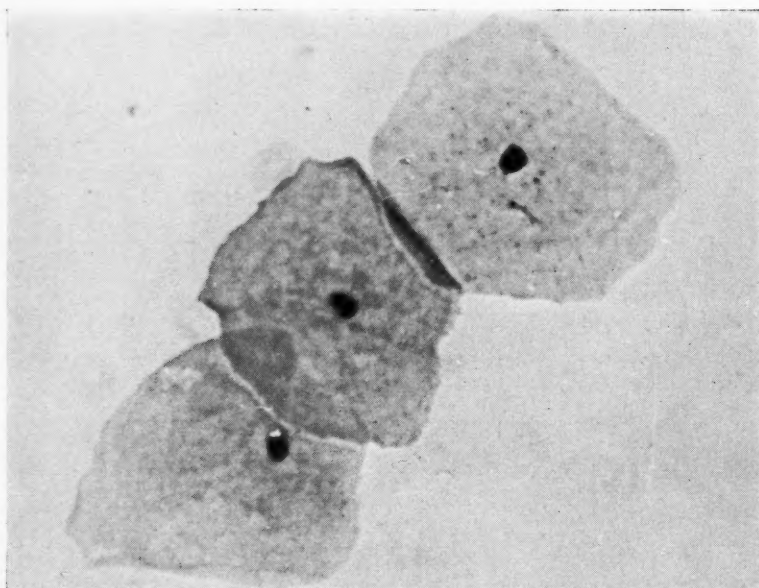


Fig. 8.—Vaginal smear of the same patient shown in Figs. 1 and 5, ninety-six hours after injection of 10 mg. estradiol benzoate and twenty-four hours after intravaginal administration of 100 mg. Terramycin. The estrogenic effect on the squamous epithelial cells which was masked twenty-four hours before because of the extensive cytolysis is now evident. The proliferation goes up to the cornified layers. The patient observed no more leukorrhea.

A great percentage of all patients do not have in their pretherapeutic findings a pure Döderlein flora. Patients in whom we find vaginitis—with or without *Trichomonas vaginalis*—with mainly cocci (Fig. 2) are usually not the ones in whom we find the posttherapeutic leukorrhea. The examination of the vaginal smears of the patients with posttherapeutic leukorrhea reveals in nearly all cases a marked cytolysis due to *B. vaginalis* (Figs. 5 and 9). If the pretherapeutic smears of these patients are checked, we can usually find a flora of *B. vaginalis* or a mixed flora with predominantly *B. vaginalis* (Figs. 1 and 2).

After estrogen administration a high proliferation and cornification of the epithelial cells are expected (Fig. 5). But in these cases where we have pretherapeutically a flora of *Bacillus vaginalis* or a mixed flora with predominantly *B. vaginalis* and a cell type which is affective to the cytolytogenic effect of the Döderlein bacilli, we observe that the destruction of cells due to these bacilli



Fig. 9.

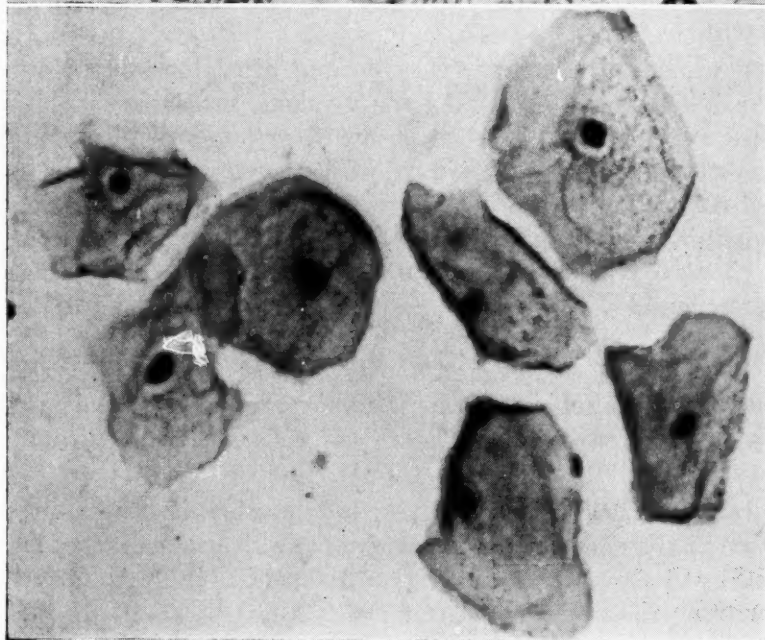
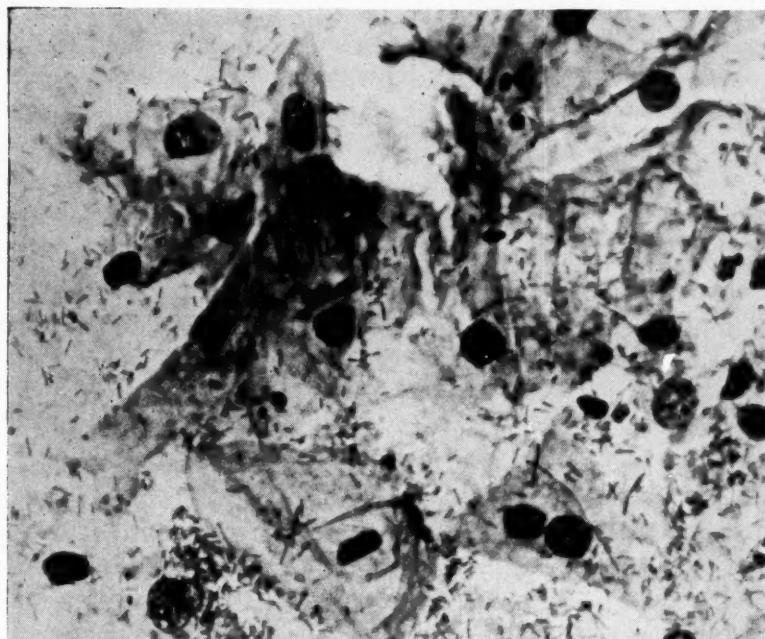


Fig. 10.

Fig. 9.—Vaginal smear of a patient (castrate) with severe menopausal symptoms. She was treated with estrogens (20 mg. estradiol valerate). Despite this estrogen administration the cells show no cornification. The cells are folded and crowded and mostly cytolized due to *Bacillus vaginalis*. The patient complained of leukorrhea.

Fig. 10.—Vaginal smear of the same patient shown in Fig. 9, twelve hours after intravaginal administration of 100 mg. Aureomycin. Most of the bacilli and the cytolytic changes have completely disappeared. The squamous epithelial cells show now the estrogenic effect which we could not identify in the smear (Fig. 9) because of the extensive cytolysis. The patient did not complain of leukorrhea after the inhibition of cytolysis.

on the surface of the epithelium is faster or at least as fast as the proliferation due to the administered estrogens. As estrogenic stimulation of the epithelium always causes a marked cellular growth it is easy to understand that the vagina is slowly covered with a white mass of cellular debris. Leukocytes are not found. The highly acid reaction and Döderlein bacilli are abundant. We decline to say that the resulting leukorrhea is one of the unexplained secretions which we "sometimes observe as a normal consequence of an estrogenic therapy."

It can be true that one of the factors of leukorrhea following estrogenic therapy is the resulting rejuvenation of the tissue and the increased production of cervical mucus. The main cause is mostly cytolysis due to *B. vaginalis*. This can be proved by administration of a bacteriostatic drug to the vagina. We used Aureomycin, Terramycin, or Chloromycetin to inhibit the *B. vaginalis*. A single intravaginal administration of 100 to 250 mg. of these drugs is enough to stop the cytolysis immediately. The proliferation of the epithelium—still stimulated by the estrogenic drug—goes suddenly up to the cornified-cell layers (Fig. 8). The cells of the cornified layers are resistant to the cytolytic effect of the Döderlein bacilli. The cytolysis and with it the posttherapeutic leukorrhea disappear in nearly all cases completely, even if the bacilli recur after the end of the bacteriostatic effect, provided that the estrogenic stimulation is still present.

During prolonged estrogenic therapy and after the end of an estrogenic effect the cytolysis may recur. As the cytologic smears show in some cases of prolonged and even very high estrogenic therapy no cornification of the cells but only cytolytic types, one could be misled to presume that cytolysis is in some direct connection with a high estrogenic effect. This is not so, of course; a single administration of a bacteriostatic drug will show that the proliferative types are changed immediately to the cornified-cell types (Figs. 9 and 10) if the cells grow without destruction.

### Conclusions

1. The leukorrhea following local, oral, or parenteral estrogenic therapy can be due to a massive destruction (cytolysis) of the superficial cells due to *Bacillus vaginalis* Döderlein.
2. Only those patients who had in their pretherapeutic smears a flora of mainly *B. vaginalis* and a cell type which is affective to the cytolytic effect of the bacilli will show the intra- or posttherapeutic cytolysis of epithelial cells and leukorrhea.
3. The cytolysis and with it the leukorrhea following estrogenic therapy disappear usually after a single intravaginal administration of a bacteriostatic drug. If the estrogenic effect is still present, the proliferation then goes up to the cornified and resistant cell layers.
4. The bacterial cytolysis is not significant for any specific hormonal situation. But as the bacterial cytolysis is bound to a distinct cell layer we can draw indirect conclusions from the presence of these cell changes.

5. In the case of prolonged estrogenic treatment the pretherapeutic smear type and the pretherapeutic bacterial flora are unimportant. As cytolysis can "mask" an estrogenic effect of the squamous epithelium concerning the cornification of the cells we should in these cases administer prior to the cytologic hormonal reading (twenty-four hours) a bacteriostatic drug for differential diagnosis.

6. As we find in most cases pretherapeutic conditions which are hostile to the growth of Döderlein bacilli and/or in which the epithelial cells are resistant to the cytolytogenic effect of these bacilli, the cytolytic changes of the vaginal epithelium and leukorrhea following estrogenic therapy can be observed only in a very limited percentage of patients treated with estrogens.

Estrogen administration can cure some cases of existing leukorrhea, e.g., in atrophic vaginitis. A prolonged intravaginal administration of antibiotics can on the other hand (in some cases) lead to damage of the healthy flora of the vagina.

### Summary

Cytolysis and a distinct type of leukorrhea can occur after estrogenic therapy and can be inhibited in many cases with a single intravaginal application of a bacteriostatic drug. The importance of cytologic and bacteriologic investigations in cases of leukorrhea prior to therapy is emphasized.

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## THE pH OF THE HUMAN UTERINE CAVITY IN SITU

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THE viability of the human egg and sperm cell depends not only on their respective genetic constitutions but on the physicochemical conditions of the environment. Of the multiple factors which may affect the survival of the human gametes and later the implantation of the zygote, the pH of the uterine secretions appears to be important. In 1933 Defrise<sup>1</sup> reported on the culture in vitro of the egg of the albino rat. From these experiments it appears that the egg during normal development is subjected to an acid environment during implantation. Hall<sup>2</sup> in 1936 showed that in both the rat and mouse the occurrence of estrus is associated with a decrease in the H-ion concentration of the uterine fluids, which reaches a maximum generally in early metestrus. This decrease in the alkalinity of the uterine fluids may be of importance to the normal development and implantation of the egg.

The purpose of this preliminary investigation was to determine electrometrically the hydrogen ion concentration of the human uterine fluids and/or mucosa in situ and to correlate the readings with the cytologic age of the endometrium.

### Materials and Methods

A group of 53 women attending the Post-natal Clinic of the Jefferson Medical College Hospital was studied. These patients were selected inasmuch as they had experienced normal postpartum courses and pelvic examination was negative. In this group were 10 postpartum amenorrheic women and 43 with established normal menses.

A specially constructed glass electrode (Fig. 1, *a*), designed for study of the uterine cavity and produced according to specifications furnished to the manufacturer, was employed in conjunction with the Beckman electrometer. In later studies this curved electrode was replaced by the Beckman stomach glass electrode 290-30 for infants (Fig. 1, *b*).

The technical aspects of the determination of the pH of the uterine cavity were carried out under aseptic conditions. Heat sterilization was employed for the instruments with the exception of the glass electrodes. The latter were immersed in a solution of Zephiran 1:1,000 or mercuric cyanide 1:4,000 for twenty minutes, followed by thorough rinsing with sterile distilled water before each application. Following a careful bimanual pelvic examination with particular reference to position of the uterine body, the external genitals and genital canal were prepared as for a surgical procedure, using the Zephiran and mercuric cyanide solutions. The cervix was exposed through a sterile bivalve speculum, all secretions wiped away, and the cervix carefully cleansed. The anterior lip then was grasped with a tenaculum forceps and the uterine cavity sounded gently. The external os was wiped dry of all secretions before introduction of the standardized curved glass electrode or the



flexible stomach electrode. The circuit was completed by a salt bridge of the reference electrode placed in contact at the external os of the cervix and the determinations made with the temperature compensator set to 37° C.

Seven readings were taken in each patient, with the electrode moved gradually toward the fundus of the uterus and full stabilization of the meter needle allowed with each change of position. Following the readings an endometrial biopsy was done and prepared in the routine manner.

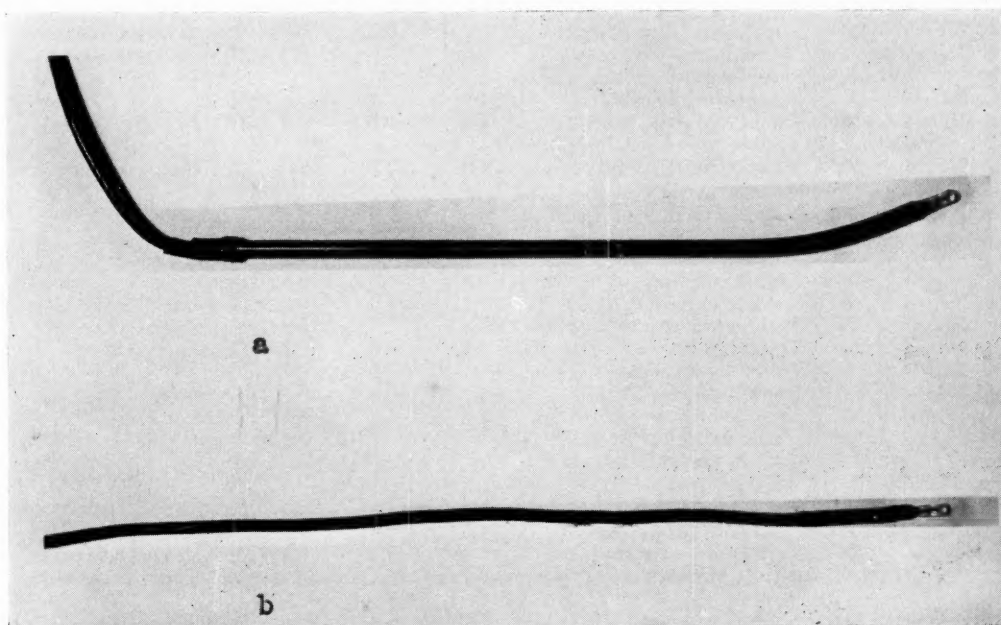


Fig. 1.—*a*, Glass electrode with the uterine curve, later replaced by *b*, the Beckman stomach glass electrode 290-30 for infants.

### Results

Patients in whom the uterine sounding or instrumental manipulations produced a sign of blood and cases in which difficulty was experienced in performing a biopsy are not included in the final data.

The results are based on the findings in 25 patients. In this group are 5 postpartum amenorrheic women and 20 patients with established normal menses. Of the latter number, 17 were returning for their last follow-up examination one year following their confinement, and 3 were 10 to 18 weeks post partum. The amenorrheic patients were returning for their first or second postnatal visit, 6 weeks to 11 months from date of delivery.

The pH and corresponding biopsy readings of the 20 normal menstruating and 5 amenorrheic patients are shown in Tables I and II, respectively. The mean pH values are presented graphically in Fig. 2. These latter values, when treated by the method of the analysis of variance, are found to differ significantly.

The lowest pH values of the uterine fluids and/or mucosa are found in patients with a secretory endometrium and the more alkaline readings correspond generally to a proliferative type of endometrium. The most alkaline readings are obtained in the postpartum amenorrheic patients. Of singular interest is Patient 15 with a mid-secretory endometrial diagnosis and the low-

TABLE I. PH AND ENDOMETRIAL BIOPSY READINGS IN PATIENTS WITH NORMAL MENSES

PATIENTS		PERTINENT DATA	pH VALUES*			CYTOLOGICAL AGE ENDOMETRIUM
RACE	AGE		INITIAL	FUNDAL	AVER- AGE	
1. Negro	20	Normal last menses	6.3	6.8	6.6	Proliferative
		12 weeks post partum	6.6	7.1	6.9	Proliferative
		Expecting menses				
2. Negro	25	Tenth day of cycle	6.9	7.0	6.9	Proliferative (early)
3. Negro	23	Eighth day of cycle	6.8	7.0	6.9	Proliferative (early)
4. Negro	27	Fourteenth day of cycle	6.7	6.9	6.8	Proliferative (early)
5. Negro	24	Normal last menses, 10 weeks post partum and expecting period	6.5	7.0	6.7	Proliferative (late)
6. Negro	19	Twenty-fourth day of cycle	6.6	6.9	6.8	Proliferative (late)
7. Negro	34	Twenty-fourth day of cycle	6.9	6.9	6.9	Proliferative (late)
8. Negro	38	Nineteenth day of cycle	6.9	6.6	6.8	Proliferative (late)
9. Negro	25	Twenty-fourth day of cycle	6.7	6.6	6.6	Secretory (early)
10. Negro	33	Eighteenth day of cycle	6.5	6.2	6.5	Secretory (early)
11. Negro	25	Twenty-first day of cycle	6.7	6.5	6.5	Secretory (early)
12. Negro	35	Eighteenth day of cycle	6.5	6.7	6.6	Secretory (early)
13. Negro	24	Thirtieth day of cycle	6.5	6.8	6.7	Secretory (late)
		menses expected				
14. White	--	Expecting period	6.2	6.6	6.5	Secretory (late)
15. White	26	Twenty-first day of cycle, menses delayed; pregnant, normal term delivery	6.0	6.6	6.4	Secretory (mid-)
16. White	28	Twenty-fifth day of cycle.	6.6	6.4	6.5	Secretory (late)
		Expecting menses	6.5	6.6	6.5	Secretory (late)
17. Negro	19	Eighteen weeks post partum. First menses ensuing	6.7	6.3	6.5	Secretory (late)
18. Negro	24	Expecting menses	6.4	6.6	6.5	Secretory (late)
19. Negro	38	Twenty-third day of cycle	7.0†	6.5	6.8	Secretory (late)
20. Negro	21	Nineteenth day of cycle	6.6	6.5	6.5	Secretory (late)

\*Initial pH value, average of first 3 potentials recorded after insertion of electrode.

FUNDAL pH value, average of last 4 potentials taken in the fundal area.

Average pH value, mean of all pH readings in the patient.

TABLE II. PH AND ENDOMETRIAL BIOPSY READINGS IN POSTPARTUM AMENORRHEIC PATIENTS

PATIENTS		PERTINENT DATA	pH VALUES			CYTOLOGICAL AGE ENDOMETRIUM
RACE	AGE		INITIAL	FUNDAL	AVERAGE	
1. Negro	27	12 weeks post partum	6.7	7.0	6.9	Insufficient material obtained
2. Negro	21	4 weeks post partum	6.9	7.0	6.9	Insufficient material obtained
3. Negro	23	8 weeks post partum	7.1	7.2	7.1	No curettings obtained
4. Negro	41	8 weeks post partum	6.6	7.2	7.1	No curettings obtained
		10 weeks post partum	6.7	7.1	6.9	No curettings obtained
		12 weeks post partum	6.8	7.3	7.1	No curettings obtained
		14 weeks post partum	6.8	7.3	7.1	No curettings obtained
5. Negro	32	32 weeks post partum	6.7	7.0	6.9	No curettings obtained
		42 weeks post partum	6.8	7.1	6.8	No curettings obtained

est pH recorded. Apparently this patient was pregnant at the time of the experiment and notwithstanding the procedure she carried to term and was delivered spontaneously of a normal infant.

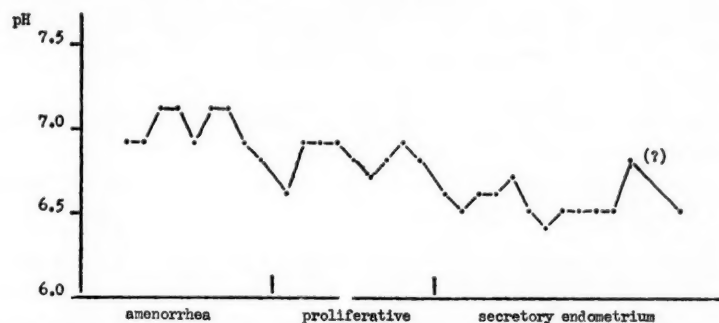


Fig. 2.—The mean H-ion concentration of the uterine contents. Vertical axis, pH values; horizontal axis, type of endometrial biopsy at time of pH observation.

### Comment

It is generally agreed that the presence of secretory changes in the endometrium is presumptive evidence of ovulation. Limited as the experiments herein reported are in number, they strongly indicate that human ovulation is accompanied by a period of relative acidity of the uterine fluids and/or mucosa. These observations are emphasized further when weekly pH readings are taken in patients during a complete menstrual cycle. There is an indication, therefore, that there is a close correspondence between the hydrogen ion concentration of the uterine fluids and/or mucosa and the stage of the endometrial cycle.

The series is too small from which to dogmatize; however, several facts have evolved. The tolerance of the patient for the method as a diagnostic procedure definitely has been established. No difficulty was encountered with introduction of the instruments, pain, or bleeding. The sensibilities of the patient and the degree of tightness of the cervical canal with its external and internal openings will determine the degree of discomfort associated with the test. When the instrument is within the uterus, the discomfort ceases or is well borne. The majority of the patients made no complaints and all stood the procedure well with very little discomfort.

Following the pH recordings, the patients were observed closely and were followed through several menses to note any late sequelae. In no case was there evidence suggestive of uterine infection. This danger is avoided by rigid asepsis and the proper selection of cases.

The determination of the pH of the uterine cavity is severely limited, however, by the nature of the measuring devices available. The manufacture of so small an electrode is technically difficult. Furthermore, the short over-all life of the tiny glass electrode made it necessary to check frequently for stability, using the regular Beckman buffer standardization with buffers pH 4.0 and pH 7.0. Nevertheless, the findings reported here are sufficiently suggestive to make

it worth while to extend the study to a larger group. A practical method of diagnostic value appears to be available, particularly important in the problem of the infertile woman.

### Summary

A method is presented for the study of the pH of the human uterine fluids and/or mucosa in situ.

The hydrogen-ion concentration of the uterine cavity varies during the normal menstrual cycle.

A decrease in the alkalinity of the uterine fluids and/or mucosa is associated with a corresponding secretory endometrium.

The occurrence of ovulation appears to be accompanied by a period of relative acidity of the uterine fluids and/or mucosa.

Appreciation is expressed to Drs. Lewis C. Scheffey and Thaddeus L. Montgomery for the facilities of their departments. I am deeply indebted to Drs. Peter A. Herbut and Robert L. Breckenridge of the Clinical Laboratories for the preparation of the biopsy material and to Messrs. E. B. Patterson, Sr., and A. E. Allgrunn of the Arthur H. Thomas Co., Philadelphia, for their constant kindly interest and valuable technical advice.

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814 PINE STREET



## OBSTETRICAL RESPONSIBILITY FOR THE MORTALITY OF THE FIRST DAY OF LIFE

### A Report of 551 Deaths

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INTEREST in neonatal mortality rates is so great that the Brooklyn Committee on Maternal Welfare has been prompted to inquire into the nature of its own problem.\* In 1952 increases in nonwhite infant mortality were recorded in Manhattan, Brooklyn, and the Bronx, but Brooklyn was the only borough of the City of New York in which infant mortality among whites had increased substantially over that in 1951. Three of the five districts of the city with the highest infant mortality rates were in Brooklyn.<sup>1</sup>

Since the mortality among infants is much higher in the first day of life than in any succeeding age group it was decided to begin with scrutiny of that increment of the neonatal death rate. And since the economic status of the family rather than that of the residence area is perhaps the most<sup>2</sup> significant factor, health districts were not studied separately.

It was felt, too, that the earlier death occurred in the neonatal period the less the pediatrician could be expected to make any significant contribution, and that accent on the management of prematurity might be of somewhat limited value in the reduction of mortality in this statistically important group.

If any considerable number of these deaths should invite a frontal attack similar to the assault so successful in the reduction of the maternal death rate, then the educational method developed in Brooklyn at obstetrical conferences on maternal deaths would be quickly available.

In 1953 there were reported 55,851 live births in the Borough of Brooklyn. Provisional figures indicate that there were 6,133 fetal deaths and a total of 1,004 neonatal deaths; 932 of these neonatal deaths occurred within a period of ten days. Transcripts of matched certificates of birth and death of 551 infants who died within twenty-four hours of birth were provided by the Commissioner of Health of the City of New York.

The length of gestation has not been tabulated since birth weight appeared to be a more reliable index of fetal maturity. It is recognized that such a definition of prematurity may lead to error, yet this criterion was thought to be sufficient for this study. The nature of the material is shown in Table I.

There were 529 mothers. In 182 cases neonatal death was the result of their first pregnancy. In 82 cases stillbirth had occurred once before; in 34 cases, twice before; in 10 cases, three times; and 7 women had had four or more stillbirths previously.

\*The Committee acknowledges with thanks the fine cooperation of Carl L. Erhardt, Director Bureau of Records and Statistics, Department of Health, City of New York.

In 92 cases, 31 white and 61 nonwhite patients, there had been no pre-natal care, and 20 of these infants were delivered by an ambulance physician either at home or on the way to the hospital. In 63 cases fetal weight was less than 1,000 grams and in but one case was fetal weight more than 2,500 grams.

TABLE I. NEONATAL DEATHS, FIRST DAY OF LIFE

WEIGHT (GRAMS)	TOTAL NO.	WHITE		NONWHITE	
		MALE	FEMALE	MALE	FEMALE
Under 400	43	11	13	10	9
400-999	191	69	39	55	28
1,000-1,499	109	55	24	23	7
1,500-1,999	50	22	14	7	7
2,000-2,499	28*	12	8	5	2
2,500-2,999	47*	22	19	3	2
3,000-3,499	39	18	12	4	5
3,500-3,999	18	11	2	3	2
4,000-4,500	4	2	2	—	—
Unknown	22	15	5	—	2
	551	237	138	110	64

\*1 sex undetermined added.

Pregnancy was multiple in 31 cases; in 20 cases both twins died, and in one case triplets died on the first day of life. In but 2 cases did the fetus weigh as much as 1,600 grams, so that premature birth was not due to over-distention of the uterus.

The influence of maternal age is not clear but since it may be a factor in neonatal death, data appear in Table II.

In 266 cases the cause of death was reported after postmortem examination. On gross examination of the fetus, erythroblastosis, birth injuries, and serious defects of the central nervous system were apparent causes of death in 24 additional cases. In 241 cases the diagnosis of prematurity or atelectasis was made clinically. If for practical purposes 145 infants in this group whose birth weights were less than 1,000 grams should be added to 176 in whom the diagnosis was based on autopsy, it may be said that death was due to inadequate functioning of the lungs in 58 per cent of all the deaths. Bundesen and Potter<sup>3</sup> call this abnormal pulmonary ventilation.

TABLE II. AGE AND RACE OF MOTHER

AGE (YEARS)	TOTAL NO.	RACE	
		WHITE	NONWHITE
Under 15	1		1
15-19	48	25	23
20-24	149	90	59
25-29	139	101	38
30-34	124	90	34
35-39	52	45	7
40-45	16	13	3
Total	529	364	165

The immediate cause of death should be certified by the pathologist. Often, however, he is unable to do so. There may be no reason for death other than the fact of premature birth; the infant may have been born too soon to live. There may be no pathological condition. It is said, and it is strictly true, that neither prematurity nor atelectasis should be classified as a cause of death. Edith Potter's work gives substance to this belief. If, on post-

mortem examination, no specific pathological lesion can be found and death can likewise be accounted for only on the basis of failure of the lungs to function because of immaturity of the tissue, it may be obvious that this will be the leading cause of death, no matter what the terminology. The causes of death are shown in Table III.

TABLE III. CAUSES OF DEATH

CAUSE	AUTOPSY	CLINICAL
Prematurity	98	190
Atelectasis	78	51
Birth injury	17	6
Congenital defects	43	14
Anoxia	15	20
Erythroblastosis	8	4
Bronchopneumonia	4	—
Hemorrhagic disease	3	—
Total	266	285

### Maternal Factors

In order to make any significant reduction in the neonatal death rate, it is desirable and necessary to explain death from an obstetrical point of view. Largely, then, even when specific physical disorders of the fetus cause death, maternal conditions should be studied. Clinical factors are not so complex that obstetrical management cannot be fairly well agreed upon.

Maternal conditions contributed directly to neonatal death usually after premature delivery in antepartum hemorrhage, toxemia, isoimmunization, syphilis, and diabetes. An infant that weighed 2,000 grams born by cesarean section after maternal death, due to cerebral hemorrhage lived but fifteen minutes. A ruptured appendix resulted in premature birth of an infant that weighed 1,000 grams. Delivery was premature in 8 cases of toxemia of pregnancy and only one fetus weighed more than 2,400 grams.

In four cases, fibromyomas of the uterus were mentioned as associated causes of death, yet in but one case in which cesarean section was performed for dystocia was the implication clear.

Antepartum hemorrhage was an important factor in 37 cases. Hemorrhage was the reason for interruption of pregnancy, and prematurity was the result in 31 cases. Only 4 infants were known to weigh 2,500 grams or more. The type of delivery and birth weights are shown in Table IV.

TABLE IV. DELIVERY FOR ANTEPARTUM HEMORRHAGE

WEIGHT (GRAMS)	TOTAL	PLACENTA PREVIA		ABRUPTIO PLACENTAE	
		PELVIC	ABDOMINAL	PELVIC	ABDOMINAL
Under 1,000	9	1	4	2	2
1,000-1,499	12		3	4	5
1,500-2,500	10		4	4	2
Over 2,500	4		2	1	1
Unknown	2				2
Total	37	1	13	11	12

### Operations for Delivery

Birth of 404 infants was spontaneous, other than for episiotomy in some instances; 69 presented by the breech. Some type of operation was performed for delivery in 147 cases. Version and some form of extraction were performed in some instances for very small infants. Severe congenital defects

(13 cases), birth injuries (13 cases), and erythroblastosis were present in 39 infants weighing over 2,500 grams delivered by operations other than cesarean section.

Cesarean section was performed on 56 women. Premature birth of a fetus weighing less than 2,500 grams was the outcome of 70 per cent of these operations. In 6 of 8 elective operations performed because of previous cesarean section, the fetus weighed less than 1,800 grams. Except for simple episiotomy the operations for delivery are listed in Table V.

TABLE V. OPERATIONS FOR DELIVERY

OPERATION	TOTAL	WEIGHT (GRAMS)				
		UNDER 1,000	1,000- 1,499	1,500- 2,500	OVER 2,500	UNKNOWN
Low forceps	43		3	11	24	5
Midforceps	3			2	1	
Version and extraction	5	3		1	1	
Manual rotation	5			1	4	
Manual dilatation	1				1	
Breech extraction	34	12	7	6	8	1
Cesarean section	56	13	8	15	17	3
Total	147	28	18	36	56	9

### Comment

It should be emphasized that this study has to do with only the first day of life. Included in the accepted categories of premature birth weight under 2,500 grams are 76 per cent of the cases. In 73 per cent of the total number of cases birth was spontaneous. In approximately 50 per cent of all 551 cases, prematurity alone appeared to be the cause of neonatal death. Perhaps this simple term connotes better than abnormal pulmonary ventilation what I have in mind. There is no doubt, however, that Potter has created an enormous interest in her two principal causes, resorption atelectasis and hyaline membrane. Neither is there any doubt that her ability to stimulate us again and again has contributed much to our knowledge of fetal pathology.

There is some evidence that severe deficiencies in diet may have an effect on the developing fetus but whether they will cause premature delivery is not certain, and little or nothing can be done significantly to reduce fetal loss from this cause. Except for the fact of premature birth, lack of prenatal care appeared to have no bearing on the fetal mortality of this series.

Obviously an important cause, congenital anomalies accounted for 10 per cent of the deaths. Though due for the most part to defects in the genes, some are the result of disease during pregnancy.

Maternal disease may cause intrauterine death or premature birth of a fetus unable to live. Rheumatic heart disease, though not found in this series, is an illustration. Erythroblastosis, though not truly a maternal disease, is actually the most important blood disease of the neonatal period. Responsibility for early recognition of isoimmunization rests upon the obstetrician. Current practice does not endorse early termination of pregnancy. The clinical condition of the infant is the best index of the severity of the disease, and



close cooperation of obstetrician and pediatrician is essential. In diabetes, fetal risk is related to the severity of the disease, the nature of treatment, and the inherent risk of cesarean section.

In the management of placenta previa it is currently good practice in most cases to carry the fetus to maturity. As in separation of the placenta, conservatism and radicalism must be balanced. If, however, we give to the fetus a greater importance than the patient's condition deserves, we put the picture out of perspective.

Intracranial hemorrhage sometimes occurs with spontaneous birth, though more often with traumatic delivery. Wide episiotomy without use of forceps is better for the premature infant, provided the second stage of labor is not unduly prolonged. Version has very little application. Even the decision to use midforceps should be weighed. Judicious use of analgesia and anesthesia, obviously fundamental, is of particular importance to the premature infant. Every effort should be made to avoid administration of sedatives prior to cesarean section. This operation of itself for reasons that are not clear appears to carry with it increased likelihood of fetal anoxia.

Obstetrical complications play an important part in fetal loss. Attention to cesarean section should produce sizable results in reduction of neonatal mortality as well as the maternal death rate.

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32 REMSEN STREET

## **CESAREAN SECTIONS AT ST. LOUIS MATERNITY HOSPITAL FROM 1948 THROUGH 1952**

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Medicine)*

THE quality of obstetrical practice in a hospital is frequently judged by the relative number of cesarean sections. Where the rate is abnormally high it is assumed, usually without any other evidence, that the quality of obstetrical practice is less than ideal. On the other hand, where the rate is low, it usually is assumed that obstetrical practice is good. Neither of these generalizations necessarily reflects the truth. That this is so is self-evident. For example, if the rate were zero many babies and some mothers would certainly lose their lives unnecessarily, and if the rate were 100 per cent, vast numbers of needless operations would be done with little likelihood of better results for either mother or child. The ideal incidence of cesarean section should be, therefore, that rate which returns the largest number of mothers safely to their homes with a normal living child. The actual rate necessary to accomplish this end must be established by careful study of results obtained in the larger obstetrical services. For this reason, we have collected the data pertaining to cesarean sections and the over-all fetal and maternal mortality at the St. Louis Maternity Hospital for the five-year period from 1948 through 1952.

The recent medical literature reveals a marked increase in cesarean section rates. A 6 per cent incidence of cesarean sections is reported from the New York Lying-In Hospital<sup>1</sup> and a recent report from San Francisco<sup>2</sup> shows rates as high as 10 per cent. The masses of data available prove without doubt that pregnancy and parturition are safer today than twenty years ago. This increased safety certainly applies to delivery by cesarean section as well as vaginal delivery. Better health of the gravid woman, better prenatal care, blood banks, and antibiotics all contribute to the remarkable decrease in maternal deaths. Perhaps even the obstetricians should be given some credit too. Many more physicians are especially trained in obstetrics now than twenty years ago and their influence is spread through virtually every community in the country. The explanation for the increased incidence of cesarean section is probably to be found in the simple fact that section is now a relatively safe method of delivery.

What new group of patients is being subjected to abdominal delivery in order to fill the gap left by the now obsolete medical indications for cesarean section? Twenty years ago heart disease and tuberculosis were thought to be

sound indications for cesarean section since abdominal delivery avoided subjecting the patient to the stresses of labor. Time has shown, however, that the stresses of labor in these patients are less serious than are the stresses of cesarean section. If this is true for the patient whose life is compromised by a serious illness, then it must also be true in the healthy gravid woman.

Are there more contracted pelves than twenty years ago? Are more sections being performed for placenta previa and premature separation of the placenta? Is cesarean section less of a risk to the mother and fetus than a midforceps delivery? Is elective section in a patient with a previous section always justifiable? Can the concept of the "valuable baby" or "premium baby" be justified as an indication for cesarean section or does it reflect an untenable concept that one life is worth more than another even prior to birth? Do we perform a service to the "elderly nullipara" by advising cesarean section or is it in reality a potential, although well-intentioned, disservice? Are section rates of 10 per cent justifiable or is it possible to practice good obstetrics with cesarean section rates equal to those reported twenty years ago? These are questions which need to be answered.

In an attempt to answer these questions the following study was undertaken. Maternal mortality and morbidity and fetal mortality in abdominal deliveries are compared with maternal mortality and morbidity and fetal mortality in vaginal deliveries. The causes of mortality were ascertained. The data obtained are compared with those presented in an earlier report from this institution<sup>3</sup> and with current reports in the medical literature from other institutions.<sup>1, 2</sup>

### Material

Data presented in this paper were collected from the records of the St. Louis Maternity Hospital. The report covers a period of time from Jan. 1, 1948, through Dec. 31, 1952. Much of the material, although obtained from the hospital records, was known to us because of consultation or other personal experience with the patient. The report from this institution with which some of the current data are compared was published in 1938 and encompassed a five-year period from 1932 through 1937.

### Incidence of Cesarean Section

From 1948 through 1952, 17,376 deliveries were performed at the St. Louis Maternity Hospital. Of this group, 407 were cesarean sections, an incidence of 2.3 per cent. The ward service cesarean section rate was 1.8 per cent and the private rate, 2.7 per cent. A yearly variation was noted in the combined cesarean section rate. The highest was noted in 1950 when the rate was 2.6 per cent, and the lowest in 1948 when the rate was 2.0 per cent. In the previously reported series from this hospital (1932-1937) there were 7,515 deliveries with 173 cesarean sections, an incidence of 2.3 per cent. The ward cesarean section rate was 1.9 per cent and that of the private service, 2.9 per cent. This comparison (Table IA) shows that the present cesarean section rate in this hospital is virtually identical with the rate reported for 1932 to 1937. This does not answer the question as to whether good obstetrical practice permits rates of this order. The answer to this question must be sought in a study of the fetal and maternal deaths.

TABLE IA. INCIDENCE OF CESAREAN SECTION\*

YEARS	DELIVERIES			CESAREAN SECTIONS		
	WARD	PRIVATE	TOTAL	WARD	PRIVATE	TOTAL
1932-1937†	4,635	2,880	7,515	90 (1.9%)	83 (2.9%)	173 (2.3%)
1948-1952	7,221	10,155	17,376	130 (1.8%)	277 (2.7%)	407 (2.3%)

\*Cesarean section includes all abdominal deliveries of 20 plus weeks' gestation.

†A Ten-Year Study of Cesarean Sections in the St. Louis Maternity Hospital.<sup>1</sup>

### Maternal Mortality

A marked decline in maternal mortality was observed in the 1948 to 1952 series as compared to the 1932-1937 report (Table IB). Four deaths occurred in 16,969 vaginal deliveries. This is an incidence of 2.4 deaths per 10,000 vaginal deliveries. In 7,342 vaginal deliveries from 1932-1937 there were 22 maternal deaths. This is an incidence of 30 deaths per 10,000 vaginal deliveries. No deaths from cesarean section occurred in the currently reported group. There was one death from cesarean section in the 1932-1937 series. This represents an incidence of 0.57 per cent, or 57 deaths per 10,000 cesarean sections. The death occurred in a cesarean section performed because of heart disease. Two patients in the current series died as a result of aspiration of vomitus while being given inhalation anesthesia. These two patients probably would not have died had they been given some form of conduction anesthesia instead of inhalation anesthesia.

TABLE IB. MATERNAL MORTALITY IN VAGINAL AND ABDOMINAL DELIVERIES

YEAR	VAGINAL DELIVERIES	MORTALITY	ABDOMINAL DELIVERIES	MORTALITY
1948-1952	16,969	4*	407	0
1932-1937	7,342	22	173	1

\*Two from aspiration during inhalation anesthesia, one from acute pyelonephritis and perinephric abscess, and one from tuberculous meningitis.

Though these figures show a constant cesarean section rate, a tenfold decrease in maternal mortality is apparent in the 1948-1952 series as compared to the maternal mortality in the 1932-1937 series. This answers one important question, can a relatively low cesarean section rate be compatible with good obstetrics as judged by the maternal mortality rate? Obviously, the answer is yes, and, further, an increase in cesarean section rate at this institution would not have decreased the maternal mortality rate.

### Indications for Cesarean Section

In the current series, the indication for cesarean section was cephalopelvic disproportion in 41 per cent of the cases (Table II). Previous cesarean section accounted for 17 per cent of the total operations. Some deviation in the incidence of previous section and cephalopelvic disproportion as indications is shown on the ward and private services. Cephalopelvic disproportion accounted for 55 per cent of the cesarean sections on the ward service as compared to 34 per cent on the private service. Previous cesarean section was the indication for surgery in 7 per cent of the ward cases as compared to 22 per cent in the private cases. Placenta previa and premature separation of the placenta were found to be indications for cesarean section in 15 per cent of the cases. The ward incidence of these indications for cesarean section was 16 per cent and on the private service the incidence was 14 per cent.

Medical indications for cesarean section were found in only two patients, in whom multiple sclerosis and chronic anterior poliomyelitis were the medi-



cal diagnoses. There were a number of cases in which section was performed in the presence of medical disease but in which the operation was indicated in the best interests of the fetus. Diabetes accounted for 29 cesarean sections with an incidence of 7 per cent. In this disease the cesarean section was accomplished in an attempt to improve fetal salvage by premature delivery of the infant. This procedure is based on the generally accepted concept that premature delivery prevents the death in utero of the fetus in the last few weeks of gestation. Fetal death in utero often occurs in the presence of chronic hypertension and chronic nephritis and because of this fact 3 sections were performed prior to term because of these diagnoses.

TABLE II. INDICATIONS FOR CESAREAN SECTION

INDICATION	WARD		PRIVATE		COMBINED	
	NO.	%	NO.	%	NO.	%
Cephalopelvic disproportion	71	55	95	34	166	41
Previous cesarean section	9	7	61	22	70	17
Placenta previa	16	12	20	7	36	9
Diabetes	9	7	20	7	29	7
Premature separation of placenta	5	4	19	7	24	6
Uterine fibroids	3	2	7	3	10	2
Abnormal presentation	1	1	8	3	9	2
Cervical dystocia	1	1	6	2	7	1
Pre-eclamptic toxemia	0	0	6	2	6	1
Previous vaginal plastic surgery	1	1	5	2	6	1
Rupture of the uterus	3	2	3	1	6	1
Uterine inertia	4	3	1	1	5	1
Sterilization	0	0	4	1	4	<1
Erythroblastosis	0	0	4	1	4	<1
Prolapsed cord	1	1	3	1	4	<1
Arthropathy of the hip	0	0	3	1	3	<1
Ovarian cysts	1	1	2	1	3	<1
Eclampsia	1	1	1	1	2	<1
Chronic glomerulonephritis	2	1	0	0	2	<1
Miscellaneous	2	1	9	3	11	4
Total	130	100	277	100	407	100

In the miscellaneous group of indications for cesarean section, the question must be asked whether failed induction, polyhydramnios, menorrhagia, serious fetal distress, and hydrocephalus were really proper reasons for cesarean section. Similarly, sterilization as a primary indication for cesarean section must be seriously questioned. This entire group accounted for about 2 per cent of the cesarean sections. Cephalopelvic disproportion, previous cesarean section, placenta previa, premature separation of the placenta, and diabetes were the indications in 80 per cent of the cesarean sections.

Comparison of the indications for cesarean section in the current series with the 1932-1937 series reveals several marked changes. Although, as previously noted, the incidence of cesarean section in the two groups is similar, the indications are not similar in incidence. Cephalopelvic disproportion accounted for 33 per cent of the indications in the 1932-1937 group, but in the 1948-1952 group this indication was noted in 41 per cent of the cesarean sections.

Medical indications were second only to pelvic contraction in the 1932-1937 series and accounted for 26 per cent of the cesarean sections. In the 1948-1952 series, medical indications in which the health of the mother was the primary concern accounted for less than 1 per cent of the reasons for cesarean section.

Placenta previa was the indication for surgery in 4 per cent of the sections in the 1932-1937 patients but occurred with an incidence of 9 per cent in the

1948-1952 group. Premature separation of the placenta occurred so infrequently in the 1932-1937 series that it was not tabulated. Premature separation of the placenta was an indication for cesarean section in 6 per cent of the current series.

Toxemia of pregnancy was the indication for cesarean section in 6 per cent of the 1932-1937 series but occurred with a frequency of less than 2 per cent in the current group of patients. Previous cesarean section was the listed indication in 2 per cent of the 1932-1937 series but was found to have increased to 17 per cent in the 1948-1952 group. Postmaturity was the given indication for 5 per cent of the cesarean sections from 1932 to 1937 but was not found to occur in the current series of patients.

These data demonstrate a change in indications for cesarean section in this hospital during the past twenty years. Decrease in the frequency of indications for cesarean section in toxemia, postmaturity, and medical disease is marked. Cephalopelvic disproportion, previous cesarean section, placenta previa, premature separation of the placenta, and diabetes (for fetal salvage) have increased in incidence as indications for cesarean section. It appears that the increase in cephalopelvic disproportion as an indication for cesarean section, in the 1948-1952 series at this hospital, is a reflection of the newer philosophy in obstetrics of resorting to abdominal delivery in borderline instances rather than subjecting the mother and fetus to a traumatic vaginal delivery. The same philosophy is applicable to the treatment of premature separation of the placenta and placenta previa. This liberalization of indications, however, has not increased the section rate at this hospital.

Comparison of indications for cesarean section at this hospital with those obtaining elsewhere reveals marked deviations in philosophy. In over 1,000 cesarean sections at various San Francisco Hospitals with cesarean section rates in the vicinity of 10 per cent, repeat cesarean section occurred in 36 per cent of the reported indications. Since this occurred in only 17 per cent of our series this may be a partial explanation of the lower rates currently found at this hospital. Cephalopelvic disproportion (including pelvic contraction) was found as an indication for cesarean section in 38 per cent of the California series as compared to the 41 per cent incidence of cephalopelvic disproportion in the St. Louis Maternity Hospital series. Placenta previa and premature separation of the placenta were listed as occurring in 6 per cent of the California series as opposed to the 15 per cent incidence in the current group from St. Louis. Elderly nullipara and heart disease, which accounted for 21 cesarean sections in the San Francisco series, were not listed as indications in the 407 cesarean sections from our series.

The current report from the New York Lying-In Hospital states that the incidence of cesarean section increased from 4.2 per cent in 1951 to 5.1 per cent in 1952. The over-all private service incidence from 1932 to 1952 was 6 per cent and the pavilion rate was 2.7 per cent. A study of the indications from 1950 to 1952 in this paper shows that 46.5 per cent of the cesarean sections were performed for cephalopelvic disproportion or previous cesarean section. There is an incidence of 26.5 per cent of cesarean section for previous cesarean section; this actually exceeds disproportion as a primary indication for section. Elderly nullipara was the listed indication in 16.6 per cent of the cases and was exceeded in frequency only by previous section and disproportion. It is apparent from these two reports that much of the increase in cesarean section incidence is the result of the increasing use of previous cesarean section as an indication for cesarean section. There is also apparent in these papers a trend toward the utilization of the elderly nullipara and the associated connotation of the "premium baby" as an indication for an ever-increasing volume of cesarean sections.

### Indications for Porro Section

Table III gives the indications in the 14 cases of cesarean section in conjunction with hysterectomy. The majority of patients were operated upon electively for the convenience of the patient with a combined delivery and hysterectomy for uterine myomas. Rupture of the uterus occasioned hysterectomy in 4 of the Porro sections. None of these patients had a history of previous cesarean section. Hysterectomy for sterilization was reported in 3 cases. Premature separation of the placenta in association with large uterine myomas was the indication in one patient. Menorrhagia was the indication for hysterectomy in the remaining patient.

TABLE III. INDICATIONS FOR SURGERY IN 14 PORRO SECTIONS

Uterine fibroids	5	36%
Rupture of the uterus	4	31%
Sterilization	3	21%
Premature separation of the placenta	1	6%
Menorrhagia	1	6%
Total	14	100%

Three per cent of the entire group of cesarean sections were accompanied by hysterectomy. This compares interestingly with the 1932-1937 series in which 66 per cent of the cesarean sections were accompanied by hysterectomy. These procedures were carried out in this earlier series for sterilization in lieu of the currently accepted practice of accomplishing the same end by bilateral tubal resection. It is noteworthy that in the current series not one hysterectomy was performed for the reason for which the Porro section was devised, namely, infection.

### Type of Cesarean Section

Ninety-two per cent of the cesarean sections were classical or low cervical. The low cervical procedure in this series was almost always the low transverse cervical operation. The classical variety of cesarean section was performed in 45 per cent of the operations and the low transverse cervical in 47 per cent of the cases. In the 1932-1937 series, 56 per cent of the abdominal deliveries were accomplished by the cervical route, with a longitudinal incision employed in about 25 per cent and a transverse cervical incision in the remaining.

An attempt was made to correlate the type of cesarean section with the resultant morbidity in the 1948-1952 series. Morbidity, in this study, was defined as an oral temperature elevation to 38° C. or over on two days of the period of postpartum hospitalization or the presence of a diagnosed morbid condition resulting from childbirth with or without a febrile response. The average length of postpartum hospitalization of the cesarean section patients was about ten days and of the vaginal delivery patients about eight days.

Table IV indicates the total morbidity from all types of delivery to be 875 morbid patients in 17,376 deliveries, or a morbidity rate of 5 per cent. The total morbidity for the cesarean section group of patients was 24 per cent. There was a 25 per cent morbidity in the low cervical cesarean section group as compared to a 19 per cent morbidity in the classical cesarean section group. There were insufficient numbers in the extraperitoneal and Porro section groups to have statistical significance.

### Maternal Morbidity

Since the data in Table IV showed a lower maternal morbidity in the classical cesarean section group than in the transverse cervical section group, an

attempt was made to establish any obvious cause for this deviation in morbidity rates. It has been the considered opinion of many obstetricians for many years that the cervical approach to the fetus is potentially less hazardous to the mother than is the classical approach. This might result in the selection of the more complicated case for transverse cervical section rather than for the classical section; this type of selection might well be reflected in the morbidity figures with an unfavorable weighting of the morbidity figures against the transverse cervical section. Conversely, under these circumstances the classical incision would be used in potentially uncomplicated cases, with a favorable weighting of the results in the direction of the classical cesarean section.

TABLE IV. THE TYPE OF CESAREAN SECTION PERFORMED AND THE ASSOCIATED MORBIDITY

	NO.	INCIDENCE	NO. MORBID	INCIDENCE
All deliveries	17,376	—	875	5%
Cesarean sections:				
Low cervical section	193	47%	48	25%
Classical section	182	45%	35	19%
Porro section	14	3%	6	43%
Extraperitoneal section	18	5%	8	44%
Total	407	100%	97	24%

With this thought in mind, the entire number of cesarean sections were divided into two groups, one group classified as "in labor" and the other "not in labor," since it has been well established that labor prior to cesarean section predisposes to maternal morbidity. The result of this grouping is given in Table V. Of the 407 cesarean sections, 145 were preceded by labor and 262 were not. There was a 16 per cent morbidity in all of the cesarean sections not preceded by labor. There was a 37 per cent morbidity in those patients whose section was done during labor. This indicated that the use of the single variable of labor to produce a predictable morbidity was satisfactory.

TABLE V. MORBIDITY IN RELATION TO ANTECEDENT LABOR AND THE TYPE OF CESAREAN SECTION

	CLASSICAL	CERVICAL	PORRO	EXTRA-PERITONEAL	TOTAL
<i>Not in Labor.</i> —					
No. of sections	142	106	10	4	262
Morbidity	21	20	2	0	43
Incidence of morbidity	15%	19%	20%	0%	16%
<i>In Labor.</i> —					
No. of sections	40	87	4	14	145
Morbidity	14	28	4	8	54
Incidence of morbidity	35%	32%	100%	57%	37%

The "not in labor" and the "in labor" groups were further classified as to the type of cesarean section performed. The classical cesarean sections in the "not in labor" group produced a morbidity rate of 15 per cent as compared to the 19 per cent morbidity found with low transverse cervical sections in the same group. When this was extended to the "in labor" group it was found that the morbidity in the classical cesarean section group was 35 per cent and that the morbidity in the low transverse cervical section group was 32 per cent. It is apparent from these observations that when a single predictable cause of morbidity is used, e.g., labor, there is no real difference in morbidity rates between the low transverse cervical section and the classical cesarean section.



In an attempt to clarify this apparently paradoxical situation further, another variable was added to the system of classification, this being prophylactic antibiotics. Prophylactic antibiotics were presumably used whenever the operator felt that there was an undue risk of potential morbidity in the patient under consideration, although it was the practice of some of the operators to extend the use of prophylactic antibiotics to all patients whose delivery was by cesarean section. Prophylactic antibiotics were defined as the use of any antibiotic preceding, during, or after cesarean section in the absence of overt infection. No specific amount of antibiotic was included in the definition. It includes those cases in which a single injection of depot penicillin was given as well as those in which various combinations of antibiotics were used before the cesarean section and for many days thereafter. There was an occasional temperature elevation causing morbidity, as herein defined, which was the result of sensitivity to penicillin. This morbidity is also included in the reported data.

It is shown in Table VI that 167 patients received prophylactic antibiotics and that 240 patients did not receive prophylactic antibiotics. The morbidity of those who did not receive prophylactic antibiotics was 22 per cent and the morbidity in the group that did was 26 per cent. When a comparison of morbidity is extended to the type of cesarean section and antibiotics it is found that in the "no prophylactic antibiotics" group the morbidity for classical cesarean section is 18 per cent and for the cervical operation is 26 per cent. In the "prophylactic antibiotics" group the morbidity for classical cesarean sections was 21 per cent and the morbidity in the cervical operation was 25 per cent.

TABLE VI. MORBIDITY IN RELATION TO THE USE OF PROPHYLACTIC ANTIBIOTICS AND THE TYPE OF CESAREAN SECTION

	CLASSICAL	CERVICAL	PORRO	EXTRA- PERITONEAL	TOTAL
<i>No Prophylactic Antibiotics.—</i>					
No. of sections	126	100	7	7	240
Morbid	23	26	2	3	54
Incidence of morbidity	18%	26%	29%	43%	22%
<i>Prophylactic Antibiotics.—</i>					
No. of sections	56	93	7	11	167
Morbid	12	22	4	5	43
Incidence of morbidity	21%	25%	57%	45%	26%

In Table VII the variable of labor was again added to the classification. This tabulation includes labor, antibiotics, type of cesarean section, and morbidity. The data indicate that regardless of the type of cesarean section or whether antibiotics are used prophylactically, maternal morbidity following cesarean section is increased when labor precedes the operation. It also indicates that the morbidity rates for the classical cesarean section and the low transverse cervical cesarean section are virtually equal despite the factors of labor or prophylactic antibiotics.

To summarize the findings concerning maternal morbidity following cesarean section, it appears that the maternal morbidity associated with cesarean section is about five times that associated with vaginal delivery. Labor prior to cesarean section was found to double the maternal morbidity. No real difference in maternal morbidity could be demonstrated between the classical cesarean section and the low transverse cervical cesarean section. Prophylactic antibiotics, as defined in this study, did not materially influence the morbidity rates. This answers an earlier question, regardless of any procedures,

operative or medical, cesarean section delivery produces a much higher maternal morbidity rate than does vaginal delivery and therefore is not as safe a procedure as vaginal delivery.

TABLE VII. MORBIDITY IN RELATION TO ANTECEDENT LABOR, TYPE OF CESAREAN SECTION, AND PROPHYLACTIC ANTIBIOTICS

TYPE OF SECTION	NOT IN LABOR		IN LABOR	
	NO.	MORBIDITY	NO.	MORBIDITY
<i>No Prophylactic Antibiotics.—</i>				
Classical	108	16 (15%)	18	7 (39%)
Cervical	65	12 (18%)	35	14 (40%)
Porro	6	1 (17%)	1	1 (100%)
Extraperitoneal	2	0 (0%)	5	3 (60%)
Total	181	29 (16%)	59	25 (42%)
<i>Prophylactic Antibiotics.—</i>				
Classical	34	5 (15%)	22	7 (32%)
Cervical	41	8 (19%)	52	14 (27%)
Porro	4	1 (25%)	3	3 (100%)
Extraperitoneal	2	0 (0%)	9	5 (55%)
Total	81	14 (17%)	86	29 (34%)

### Fetal Mortality

In 17,376 deliveries of all types there were 619 fetal deaths (Table VIII). This is an incidence of 3.6 per cent. The fetal death rate in the 1932-1937 series was 4.6 per cent. When transposed in terms of babies actually saved, it represents, on the basis of the current series, an increased salvage of 180 babies. The neonatal and stillbirth rates in the current series were 1.5 and 2.1 per cent, respectively. In the 1932-1937 series the neonatal death rate was 1.8 per cent and the stillbirth rate was 2.8 per cent. Although there was an appreciable decrease in fetal mortality in both groups, the greatest decrease was in the stillbirth rate.

TABLE VIII. FETAL MORTALITY IN ABDOMINAL AND VAGINAL DELIVERIES

			NEONATAL DEATHS		STILLBIRTHS		PERINATAL DEATHS	
<i>All Deliveries.—</i>								
1948-1952	17,376		258	1.5%	361	2.1%	619	3.6%
1932-1937	7,515		138	1.8%	212	2.8%	350	4.6%
<i>Cesarean Sections.—</i>								
1948-1952	407	2.3%	20	4.9%	19	4.7%	39	9.6%
1932-1937	173	2.3%	—		—		10	5.8%

The perinatal death rate in the cesarean section deliveries was much higher than in the deliveries of all types. Thirty-nine infants were lost with a perinatal death rate of 9.6 per cent, 4.9 per cent were neonatal deaths and 4.7 per cent were stillbirths. It is interesting that the cesarean section perinatal death rate in the 1932-1937 series was only 5.8 per cent, which is approximately half of the currently reported rate.

In an attempt to explain the poor fetal salvage in the current as compared to the earlier series, the obstetrical diagnoses associated with the 39 fetal deaths were compiled. From this (Table IX) it is seen that 64 per cent of the fetal deaths were associated with obstetrical catastrophe such as placenta previa, premature separation of the placenta, and rupture of the uterus. In these situations the fetus was often dead or seriously compromised prior to delivery and the cesarean section was performed as a lifesaving measure for the mother. When the indications for cesarean section in the current series

are compared to those in the 1932-1937 series it is at once apparent that these obstetrical emergencies accounted for only 4 per cent of the operations in the earlier series as compared to 16 per cent in the 1948-1952 group. Therefore the change in indications for cesarean section has necessarily resulted in a higher fetal death rate because of the accumulation of a potentially less salvable group of fetuses, many of whom were dead prior to cesarean section.

TABLE IX. FETAL RESULTS AND ASSOCIATED DIAGNOSES IN CESAREAN SECTION

DIAGNOSIS	STILLBIRTHS		NEONATAL		PERINATAL		SURVIVAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Premature separation of the placenta	8	41	6	30	14	36	10	42
Placenta previa	2	10	4	20	6	15	30	83
Rupture of the uterus	5	26	0		5	13	1	17
Prolonged labor (dystocia)*	1	5	4	20	5	13	177	97
Previous section	0	0	2 (prem.)	10	2	5	68	97
Diabetes	1	5	2	10	3	8	26	90
Prolapsed umbilical cord	1	5	0	0	1	3	3	75
Erythroblastosis	1	5	1	5	2	5	2	50
Hydrocephalus	0	0	1	5	1	3	0	0
Other diagnoses	0	0	0	0	0	0	51	100
Total	19	100	20	100	39	100	368	

\*Cephalopelvic disproportion 166; cervical dystocia 7; abnormal presentation 9. Total 182.

There are, however, several deaths in the current series which were, at least on theoretical grounds, preventable. Outstanding in this group were 2 infants whose mothers were sectioned electively because of previous cesarean section. The operations were performed at a poorly advised period of gestation with resultant prematurity of the fetuses. Each weighed less than 2,000 grams and each died shortly after delivery. Five other infants were considered to have died as the result of poor obstetrical judgment. These were cases in which there was cephalopelvic disproportion but in which the trial of labor was too long or too vigorous so that, when labor was terminated by cesarean section, the life of the fetus was already compromised, resulting in one intrapartum death and 4 neonatal deaths. These infants accounted for 18 per cent of the cesarean section perinatal fetal mortality. In the one instance in which cesarean section was performed for hydrocephalus the infant died soon after delivery.

When the fetal salvage rate is compared to the indication for cesarean section (Table IX), it is apparent that cesarean section for premature separation of the placenta was associated with a fetal salvage of only 41.7 per cent. Placenta previa as an indication was associated with 83.3 per cent fetal salvage.

TABLE X. ANALYSIS OF 200 CONSECUTIVE FETAL DEATHS WHICH OCCURRED IN DELIVERIES OF ALL TYPES FROM JAN. 1, 1951, TO AUG. 15, 1952

I. Stillborn macerated fetuses weighing less than 2,000 grams	44	22.0%
II. Stillborn macerated fetuses weighing more than 2,000 grams	19	9.5%
III. Stillborn not macerated fetuses weighing less than 2,000 grams	16	8.0%
IV. Stillborn not macerated fetuses weighing more than 2,000 grams	36	18.0%
Total stillborn	115	57.5%
V. Neonatal deaths in fetuses weighing less than 2,000 grams	49	24.5%
VI. Neonatal deaths in fetuses weighing more than 2,000 grams	36	18.0%
Total neonatal deaths	85	42.5%
Total fetal deaths	200	100.0%

Rupture of the uterus was associated with a fetal salvage of 16.7 per cent. The fetal salvage in repeat elective cesarean section was 97.1 per cent. There were 29 cesarean sections performed for diabetes with a fetal salvage rate of 89.7 per cent. Stilbestrol or progesterone was not used routinely in the prenatal care of these diabetic patients. Cesarean section in 4 patients with erythroblastosis resulted in 2 fetal deaths. Erythroblastosis is not currently considered to be an indication for the operative premature delivery of affected infants.

Answering the question as to whether cesarean section offers a greater hazard to the life of the fetus than does delivery per vaginam, at first glance,

TABLE XI. CAUSES OF DEATH IN STILLBIRTHS

<i>44 Macerated Fetuses Weighing Less Than 2,000 Grams.—</i>	
Unknown	36
Multiple pregnancy	3
Toxemia of pregnancy	1
Cord about the fetal neck	1
Chronic renal disease	1
Erythroblastosis	2
Total	44
<i>19 Macerated Fetuses Weighing More Than 2,000 Grams.—</i>	
Unknown	7
Multiple pregnancy	4
Fetal anomalies	3
Cord about the fetal neck	2
Erythroblastosis	1
Syphilis	1
Diabetes	1*
Total	19
<i>16 Nonmacerated Fetuses Weighing Less Than 2,000 Grams.—</i>	
Unknown	5
Fetal anomalies	4
Toxemia of pregnancy	2
Multiple pregnancy	1
Premature separation of the placenta (vaginal delivery)	1
Maternal chronic arterial hypertension	1
Prolapsed cord	1
Uterine myoma	1
Total	16
<i>36 Nonmacerated Fetuses Weighing More Than 2,000 Grams.—</i>	
Unknown	8
Fetal anomalies	3
Erythroblastosis	4
Traumatic delivery	6
Excessive fetal size	1†
Brow presentation in small pelvis	1†
Traumatic forceps in small pelvis	1†
Shoulder presentation	1†
Primigravida, breech	1‡
Instrumental rotation of head	1‡
Cord about the fetal neck	3
Spontaneous rupture of the uterus	3
Premature separation of the placenta	5§
Placenta previa with cesarean section	1
Toxemia of pregnancy	1
Prolapsed cord	2
Total	36

\*Premature delivery indicated.

†Cesarean section should have been performed.

‡Cesarean section not indicated.

§Cesarean section in one patient in this group.



with a cesarean section fetal mortality of 9.6 per cent as compared to a rate for all deliveries of 3.6 per cent, it appears as if section is more dangerous to the fetus. This is not a fair comparison since many of the fetuses in the cesarean section group were dead prior to cesarean section. A comparison is then made of the "all delivery" neonatal mortality, with the repeat elective cesarean section group, since these infants were potentially salvable. It is apparent from this comparison that 2.9 per cent of the fetuses delivered by cesarean section on an elective basis because of previous cesarean section died in the neonatal period. The "all types of delivery" neonatal death rate was only 1.5 per cent and this includes all neonatal deaths regardless of the real or potential complications that might lead to neonatal death. It must be said, on the basis of this experience at this hospital, that cesarean section is a very real hazard to the life of the fetus and is greater than the danger to fetal life from vaginal delivery.

### Fetal Deaths

It was considered important in the final analysis of the cesarean section statistics at this hospital to determine whether or not an increased frequency in the section rate would have resulted in a higher fetal salvage rate. To this end 200 consecutive fetal deaths from all causes and following all types of deliveries were analyzed. These deaths occurred between Jan. 1, 1951, and Aug. 15, 1952. This represented a random sampling of 32 per cent of all the fetal deaths that occurred during the period of time encompassed by the study.

TABLE XII. CAUSES OF NEONATAL DEATHS

	FETAL WEIGHTS	
	LESS THAN 2,000 GRAMS	MORE THAN 2,000 GRAMS
Fetal anomalies	6	7
Fetal atelectasis	28	4
Fetal pneumonia	2	2
Fetal intracranial hemorrhage	2	2
Erythroblastosis	2	2
Maternal diabetes	1	2*
Premature separation of the placenta	3†	—
Multiple pregnancy	2	—
Circumvallate placenta	1	—
Elective cesarean section, premature fetus	1	—
Placenta previa with cesarean section	1	3
Maternal sickle-cell anemia	—	1
Unknown	—	3
Traumatic delivery		10
Breech presentation	—	4‡
Prolonged labor in contracted pelvis	—	2§
Face presentation	—	1‡
Prolapsed cord with version and extraction	—	2‡
Shoulder presentation with version and extraction	—	1‡
Total	49	36

\*With premature cesarean section.

†Cesarean section in one patient in this group.

‡Cesarean section not indicated.

§Cesarean section should have been performed earlier.

The results of this analysis are given in Tables X to XII. In Table XI is listed a potentially preventable fetal death. This occurred in a diabetic mother in whom pregnancy was allowed to progress to term and during the last week of gestation the fetus died in utero. It is suggested that premature delivery of this fetus either by induction or cesarean section was indicated. Also listed in Table XI under traumatic deliveries are 4 stillborn fetuses that

were considered in retrospect to have been better delivered by cesarean section. Severe trauma to the mother was sustained in one of the deliveries in which the fetal weight exceeded 6,000 grams and the mother underwent an annular detachment of the cervix.

In Table XII are listed 2 infants in whom it was thought that more acute obstetrical judgment would have resulted in fetal salvage. These two fetuses were delivered by cesarean section after prolonged labor in contracted pelvis. It was considered that earlier cesarean section was indicated. From the data obtained in these 200 consecutive fetal deaths it is apparent that in 4 instances cesarean section was indicated when not performed and might well have resulted in living babies. In 2 instances, cesarean section was performed but should have been resorted to earlier in labor. This indicates that 2 per cent of the fetal deaths were in our opinion preventable by cesarean section.

Interpolation of these findings to the entire series shows that if, in the entire perinatal mortality of 619, 2 per cent of these were preventable by cesarean section, then 12 more cesarean sections would have been indicated in addition to the 407 reported. Under these circumstances the cesarean section rate would have been increased from 2.3 per cent to 2.4 per cent.

### Summary

The cesarean section rate at this hospital from 1948 to 1952 was 2.3 per cent. This is identical with the cesarean section rate from 1932 to 1937. There have been marked changes in indications for cesarean section. Medical indications, postmaturity, and toxemia of pregnancy have occurred less frequently as indications and cephalopelvic disproportion, previous cesarean section, premature separation of the placenta, and placenta previa have increased in frequency. Comparison of currently accepted indications for cesarean section at this hospital with indications prevalent in other hospitals with cesarean section rates of 6 to 10 per cent reveals that the latter institutions have a greatly increased incidence of previous cesarean section and elderly nullipara as reasons for cesarean section. Cephalopelvic disproportion as a primary indication for cesarean section occurs more frequently in the current St. Louis Maternity Hospital statistics than in statistics reported in the previously mentioned papers.

Despite the relatively low cesarean section rate at this hospital, the maternal mortality rate was 2.4 per 10,000 vaginal deliveries and none in the cesarean section deliveries. The maternal mortality in the 1932-1937 series at this hospital was 30 deaths per 10,000 vaginal deliveries. The cesarean section maternal mortality was 57 deaths per 10,000 cesarean sections. The perinatal fetal mortality has decreased from 4.6 per cent in the 1932-1937 series to 3.6 per cent in the current series. The perinatal mortality following cesarean section in the 1948-1952 series was 9.6 per cent as compared to the 5.8 per cent reported in the 1932-1937 series. This is the result of the change in indications for cesarean section in the current series, with many infants dead or compromised prior to the cesarean section.

Despite the use of various operative techniques and prophylactic antibiotics the maternal morbidity in cesarean section patients is about five times that in deliveries of all types. There was no demonstrable decrease in maternal

morbidity when the low transverse cervical cesarean section was used as compared to the morbidity following the use of the classical cesarean section. Maternal morbidity in cesarean sections preceded by labor was about twice that of cesarean sections not preceded by labor.

The neonatal fetal mortality in elective cesarean section because of previous cesarean section was 2.9 per cent as compared to the neonatal mortality in deliveries of all types of 1.5 per cent. Analysis of the fetal deaths that occurred in all types of deliveries indicates that cesarean section was indicated but not done in 2 per cent of the cases of fetal death. If cesarean section had been accomplished in these instances the cesarean section rate would have been increased from 2.3 to 2.4 per cent.

### Conclusion

According to this analysis it is possible to practice good obstetrics with cesarean section rates equal to those reported twenty years ago and with a good result as judged by maternal mortality and morbidity and fetal mortality. Cesarean section is an increased hazard to the mother and fetus and therefore the original conservatism lauded in earlier days is still a tenable concept.

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## RUPTURED UTERI AT THE WOMAN'S HOSPITAL\*

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**R**UPTURE of the uterus is a serious, often tragic, but fortunately rather rare obstetrical complication. In the thirty-two years, from 1921 through 1952, at the Woman's Hospital there have been 36 cases in 57,167 deliveries, an incidence of one in approximately 1,588 deliveries (Table I). This compares with four series quoted by Eastman<sup>1</sup> with an incidence of one in 1,627 deliveries and an incidence of one in 1,600 deliveries at the Chicago Lying-in Hospital.<sup>2</sup>

TABLE I. RUPTURED UTERUS, WOMAN'S HOSPITAL, 1921-1952

Total No. of Deliveries		57,167
Ruptured uteri		36
Incidence		1 in 1,588
Age range	24 to 43 years	
Average age	31.5 years	
	NO.	PER CENT
<i>Parity.</i> —		
Multiparas	31	86.1
Primiparas	5	13.9
Total	36	100.0
<i>Type of Rupture.</i> —		
Spontaneous	28*	77.8
Traumatic	8	22.2
Total	36	100.0

\*Includes 13 incomplete or silent ruptures.

There were 4 maternal deaths in this series, a maternal mortality of 11.1 per cent and 11 stillbirths and one neonatal death, a fetal mortality of 33.3 per cent. Five of these patients were primiparas, and the remaining 31 were multiparas. The youngest patient in the group was 24 years old, and the oldest 43 years, with an average age of 31.5 years. Eight of these patients had traumatic ruptures, while the remaining 28 were spontaneous. Included in this latter group were 13 of the so-called "silent" type discovered at repeated elective cesarean sections.

There are certain predisposing factors to obstetrical rupture of the uterus. The outstanding factor in this series is previous cesarean section. Twenty-two, or 61.1 per cent, of these women had been previously delivered by cesarean section. Fourteen of these operations were of the low flap Munro-Kerr type and 8 were classical. Although rupture of the uterus is much more frequent after classical than low flap operations, the smaller number of ruptures fol-

\*Presented at a meeting of the New York Obstetrical Society, Jan. 12, 1954.



lowing classical operations in this series is probably due to the relative frequency with which the low flap operation is done in comparison to the classical operation at the Woman's Hospital (Table II).

This brings up the question of how to handle subsequent deliveries in a patient who has previously been delivered by cesarean section. Most authorities are in general agreement that in a patient who has inadequate pelvic measurements and obvious disproportion requiring delivery by cesarean section, she should be delivered by cesarean section in all subsequent pregnancies. The question arises, however, as to delivery in the future of the patient who has a perfectly adequate pelvis as demonstrated by one or more vaginal deliveries of average-sized babies and who is then delivered by cesarean section for placenta previa. This question also applies to the patient whose first pregnancy has been terminated by cesarean section for placenta previa and whose pelvis is adequate by x-ray pelvimetry. In general, the policy at the Woman's Hospital for many years has been "once a cesarean, always a cesarean," regardless of the indications of the original section. This policy undoubtedly accounts for the high cesarean section rate at the Woman's Hospital (12.6 per cent in 1951, 13.4 per cent in 1952, and 12.9 per cent in 1953) but it is felt that quite a few ruptures of the uterus have thereby been avoided.

Occasionally, of course, a patient with a perfectly adequate pelvis who is scheduled for a repeat elective cesarean section will go into labor spontaneously ten days to two weeks before her estimated date of confinement. Upon arrival at the hospital in active labor, examination may show the vertex at the spines with the cervix almost completely effaced and dilatation progressing rapidly. Such a patient is not rushed to the operating room for immediate section, but is allowed to continue in labor and watched carefully for signs of real or impending rupture. Her labor is then terminated by prophylactic low forceps as soon as feasible.

Several brief case abstracts of patients who were not handled by this policy are illustrative.

CASE 16.—This patient had had three uncomplicated vaginal deliveries. Her fourth pregnancy, a twin pregnancy, was terminated by classical cesarean section for placenta previa at term. Her fifth pregnancy was also a twin pregnancy and she was admitted to the hospital at term, though not in labor, for treatment of mild pre-eclamptic toxemia. Her blood pressure on admission was 160/100 and there was a trace of albumin in the urine. After three days of treatment, the toxemia cleared and induction of labor was attempted with castor oil and several small doses of Pitocin. This resulted only in mild irregular uterine contractions which subsided in a few hours. The next day, while in bed on the ward, the patient experienced sudden sharp lower abdominal pain associated with slight vaginal bleeding. At operation the old uterine scar was completely ruptured in its entire length. One twin protruded through the uterus except for its head which was still in the uterus. The other twin and placenta were found in the upper abdomen under the liver. Both were stillborn. A supracervical hysterectomy was done and the patient made an uneventful recovery.

CASE 17.—This patient had had one previous pregnancy with delivery by low flap cesarean section at term after 24 hours of labor. This operation was done in another hospital and the indications were not stated, but was probably done because of disproportion. With her next pregnancy, she went to term and was allowed to go into labor

TABLE II. RUPTURED UTERUS FOLLOWING PREVIOUS CESAREAN SECTION

ORIGINAL CESAREAN SECTION				SUBSEQUENT DELIVERY BEFORE UTERINE RUPTURE				DURATION OF LABOR AT TIME OF RUPTURE			
INDICATION	NO.	TYPE		VAG.	CESAREAN		NONE	2-3 HR.	3-4 HR.	10-12 HR.	
		LOW FLAP	CLASSICAL		LOW FLAP	CLASSICAL					
Placenta previa	9	6	3	1	2	0	7	1	1	0	
Disproportion	7	4	3	0	1	0	3	1	1	2	
Previous myomectomy	3	1	2	0	0	0	2	0	1	0	
Pre-eclamptic toxemia	2	2	0	0	0	0	1	0	1	0	
Post-maturity, age 35	1	1	0	0	0	0	0	1	0	0	
7 year treatment for sterility with amputation of cervix											
Total	22	14	8	1	3	0	13	3	4	2	

ORIGINAL CESAREAN SECTION	AT W. H.		ELSEWHERE
Low flap	9		5
Classical	3		5
Total	12		10

All patients at or near term except one para i, gravida ii, with spontaneous uterine rupture at 29 weeks' gestation after 3 hours of mild irregular labor. Had had previous classical section for placenta previa.

All patients at or near term except one para i, gravida ii, with spontaneous uterine rupture at 29 weeks' gestation after 3 hours of mild irregular labor. Had had previous classical section for placenta previa.

spontaneously. After about 12 hours of mild labor, the patient experienced sudden, severe abdominal pain with moderately profuse vaginal bleeding. At operation, a considerable amount of blood was found under the bladder flap and the musculature of the uterus was completely and widely separated the entire length of the old incision. The baby survived and it was possible to repair the rupture without removing the uterus.

CASE 22.—This patient had had three vaginal deliveries. With her fourth pregnancy she had a placenta previa at term and was delivered by classical cesarean section. She then carried to term with her fifth pregnancy and was allowed to go into labor spontaneously. After thirteen hours of labor she was delivered spontaneously. With her sixth and final pregnancy, she went to term and was again allowed to go into labor spontaneously. After ten hours of moderate labor, the uterus ruptured. At operation, an estimated 1,000 c.c. of blood was found in the peritoneal cavity and the old classical cesarean section scar was completely ruptured. The baby was stillborn. A total hysterectomy was done and the patient recovered.

Schmitz and Gajewski,<sup>3</sup> in a recent article on vaginal delivery after cesarean section, state that a "trial of labor seems indicated as the management of choice in a certain number of properly evaluated patients when supervised by a competent obstetrician in a hospital equipped to meet all emergencies." It is extremely difficult or even impossible, however, to determine which patients will have a strong, well-healed uterine scar even after an entirely uneventful postoperative course with no morbidity. The present-day safety with which cesarean section is done in recognized obstetrical hospitals should influence one in making this procedure the method of choice in delivering patients who have had previous sections. The last cesarean section death at the Woman's Hospital occurred in May, 1948. This death was directly attributable to spinal anesthesia, as the patient died on the operating table before the skin incision was completed. Since then we have performed 2,001 consecutive cesarean sections without a death through Dec. 31, 1953.

Another predisposing factor to rupture of the uterus may be generally termed a complicated delivery. By complicated is meant any delivery other than spontaneous or by prophylactic low forceps. This includes the use of high forceps, such maneuvers as version and extractions, and the deliveries of infants in abnormal presentation, such as breech. These ruptures are invariably traumatic in origin. As previously stated, there were 8 ruptures of this type in the series and several of them occurred in the early years when delivery by version and extraction enjoyed such great popularity. Three of these patients were delivered by this means. Three other ruptures occurred in the course of breech deliveries and one rupture was produced by a large abdominal tumor in the baby making delivery of the baby's body very difficult and causing bilateral tears in the lower uterine segment. One traumatic rupture occurred in the attempted rotation of a head in the occipitoposterior position with the use of Kielland forceps in midpelvis.

I make a point of exploring the uterine cavity routinely after any but a spontaneous or prophylactic low forceps delivery or after the delivery of any infant in an abnormal presentation. In these days of blood banks, chemotherapy, and antibiotics the risk of shock or infection from immediate postpartum intrauterine exploration need not be considered serious. Dieckmann<sup>4</sup>

makes the following statement on intrauterine manipulation: "Some of the maternal mortality due to postpartum hemorrhage must be charged to various obstetricians who teach that the postpartum uterus must not be invaded without a life or death indication because of the possibility of infection. If doctors will learn that it can be explored without any increase in morbidity or mortality, providing proper aseptic precautions are used, they will have less hesitancy in examining the interior of the uterus whenever there are any complications."

One patient (Case 6) was delivered at term spontaneously, of an infant in frank breech presentation. There were no apparent signs of uterine rupture and the uterine cavity was not explored. The patient was returned to bed and very gradually went into shock. Eight hours after delivery, a laparotomy was done and a complete rupture in the fundus was found at the site of a previous myomectomy. A supracervical hysterectomy was performed and the patient recovered.

Another patient (Case 7) was delivered at term by rupture of the membranes when the cervix was fully dilated, by mild traction on the feet of an infant in double footling presentation. The delivery was easy and required only 12 minutes. There was no bleeding or other apparent sign of uterine rupture. Exploration, however, revealed a tear in the right posterolateral portion of the cervix extending through the vault of the vagina and into the right lower uterine segment and out into the right broad ligament. A supracervical hysterectomy was immediately performed and the patient recovered.

A third predisposing factor to rupture of the uterus is previous myomectomy. Three patients in this series had previously had this operation. It is impossible to generalize on whether or not a patient who has had a previous myomectomy should be delivered by cesarean section. Certainly a pedunculated myoma or a subperitoneal myoma which can readily be removed without deep incision of the myometrium of the uterus could hardly be considered an indication for cesarean section. When the myoma is intramural or submucous and deep incision of the myometrium or penetration of the uterine cavity is necessary to remove the tumor, this is a different matter. It has been the custom at the Woman's Hospital for many years for the surgeon performing the myomectomy to state in his operative dictation whether or not in his opinion the patient should be delivered by cesarean section if she should subsequently become pregnant. In certain cases, therefore, previous myomectomy should certainly be an indication for cesarean section. If patients with previous myomectomies are allowed to go into labor, they should be watched very carefully and provisions should be available for immediate operation in case of real or impending rupture.

One of these cases (Case 6) has been mentioned under breech deliveries. The other two patients (Cases 2 and 26) were silent ruptures found at repeat cesarean sections and were located in the site of the previous myomectomy scars while the previous cesarean section scars remained firm and intact.

Last but not least is the perfectly normal multipara who has had one or more easy vaginal deliveries and whose uterus, during her next labor, will suddenly and spontaneously rupture.

There were two such patients in this series (Cases 10 and 28) whose history and clinical course were quite similar. Neither patient had been previously operated upon



and both had had two normal labors and uncomplicated deliveries. Both went to term with the third pregnancy and went into labor spontaneously and their uteri ruptured suddenly and spontaneously, in the first patient a very short time after the onset of labor, and in the second when fully dilated and deliverable. Both patients had stillborn babies and both patients died, the first four hours after a hysterectomy and the second on the delivery table. This last patient went so rapidly into deep, irreversible shock despite all present-day types of treatment, that she was never in condition to withstand laparotomy and died about one hour after delivery.

TABLE III. DATA REGARDING MATERNAL DEATHS  
No. of ruptured uteri treated 36. Maternal deaths 4, or 11.1 per cent.

NO.	AGE	GRAVIDITY	PARITY	LENGTH OF GESTATION (WEEKS)	CAUSE OF RUPTURE	DEATH	
						POSTPARTUM DAY	CAUSE
1	27	1	0	40	Version and breech extraction	Third	Septicemia
2	42	2	1	40	Abdominal tumor in fetus	Day of delivery	Hemorrhage and shock
3	25	3	2	40	Spontaneous	Day of delivery	Hemorrhage and shock
4	32	3	2	41	Spontaneous	Day of delivery	Hemorrhage and shock

TABLE IV. SUMMARY OF FETAL LOSS  
Stillbirths 11, neonatal deaths 1. Total 12, or 33.3 per cent.

CAUSE OF FETAL DEATH*	METHOD OF DELIVERY					NO.
	LOW FORCEPS	BREECH		ROT. OF HEAD SCANZONI	DELIVERY BY ABDOMINAL ROUTE	
		EXT.	VERSION AND EXT.			
<i>Stillbirths.—</i>						
Intrauterine asphyxia		1		1	5†	7
Intrauterine asphyxia and Prolapsed cord 1 Hydrocephalus 1			2			2
Prematurity (29 wks. gest.)					1	1
Abd. tumor in fetus (originating in bile ducts)	1					1
<i>Neonatal.—</i>						
Intrauterine asphyxia					1	1
Total	1	1	2	1	7	12

\*Eleven of 12 infants in this group were at or near term.

†Includes 1 after attempted rotation of head with Kielland forceps.

As to the treatment of obstetrical rupture of the uterus, prophylaxis plays an important part. As previously stated, 22, or 61.1 per cent, of the ruptures in this series occurred in patients who had previously been delivered by cesarean section. In order to prevent this complication, it therefore seems safer to pursue a policy of "once a cesarean, always a cesarean." Furthermore, the avoidance of such traumatizing obstetrical maneuvers as version and extraction and high forceps is also important in the prevention of rupture of the uterus. The hazards of delivering infants in breech presentation must also be borne in mind and due care exercised.

In the active treatment of rupture of the uterus, one might say, "Time is of the essence." In those cases of incomplete "silent" ruptures discovered at repeated cesarean sections, it is, of course, a simple matter to trim back the edges of the separation until fresh, healthy myometrium is encountered and repair the defect. When complete traumatic or spontaneous rupture occurs, however, immediate and often radical treatment is indicated. In some of the early cases in this series, the treatment consisted merely of packing the uterus and administering ergot preparations and stimulants. These patients either died of sepsis or shock or both, or had protracted hospitalization and eventually required extensive pelvic surgery. Nowadays, however, with adequate transfusion facilities, chemotherapy, and antibiotics available, one can usually operate on these patients as soon as the diagnosis is made.

At operation, one can occasionally be conservative and need only repair the laceration of the uterine wall. In the large majority of cases, however, the ruptures are quite extensive and hysterectomy, either complete or supracervical, is indicated. Since a complete hysterectomy always requires a little more time than a supracervical operation, the decision as to whether or not to remove the cervix rests mainly on the patient's condition. In this series, hysterectomy was done in 15 cases, 3 being complete hysterectomies while the remainder were of the quicker supracervical type.

### Summary

Thirty-six cases of obstetrical rupture of the uterus over a thirty-two-year period at the Woman's Hospital are presented. As over half of these ruptures occurred in patients who had previously been delivered by cesarean section, it therefore seems wiser to pursue a policy of "once a cesarean, always a cesarean." Granted that some patients with adequate pelvis may safely be delivered vaginally following previous cesarean section, this fact, nevertheless, should not give one a sense of false security, as it is no guarantee that the uterus of such a patient will not rupture during a subsequent labor.

Other predisposing factors such as previous myomectomies and complicated vaginal deliveries are also discussed and certain recommendations made.

TABLE V. SUMMARY OF MANAGEMENT OF 36 CASES AND OUTCOME OF TREATMENT

TREATMENT		OUTCOME OF TREATMENT				
OPERATIVE PROCEDURES	NO.	MOTHERS		BABIES		
		SATISFACTORY	DEATHS	NORMAL INFANT	STILL-BIRTH	NEONATAL DEATHS
Cesarean section and repair of defect or rupture	19	19	0	18	0	1
Hysterectomy, supracervical	12	10	2	4	8	0
Hysterectomy, complete	3	3	0	2	1	0
Vaginal deliveries with packing and supportive measures only	2	0	2	0	2	0
Total	36	32	4	24	11	1

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### Discussion

DR. JOSEPH P. DONNELLY.—From 1931 until Jan. 1, 1954, rupture of the uterus occurred 58 times in 154,000 deliveries at the Margaret Hague Hospital, an incidence of one in every 2,662 deliveries.

Of the 58 ruptures, 17 were traumatic, 18 were spontaneous, and 23 occurred in scars of previous cesarean sections. There were 11 maternal deaths in the 58 cases of rupture, a maternal mortality of 21 per cent. There were 6 deaths in the traumatic group, 5 in the spontaneous, and no deaths among the ruptures of previous cesarean section scars. The last maternal death occurred in 1943. Since that date, there has not been a death in 27 ruptures of the uterus.

Version and extraction was the cause of 10 cases of traumatic rupture; and also of 5 of the 6 maternal deaths which occurred in the traumatic group. Version and extraction has been a very dangerous procedure, at least at the Margaret Hague, and it has been very rarely performed in the past fifteen years. Craniotomy on an unengaged head and manual manipulation of the cervix have long been abandoned, and cesarean section has replaced difficult vaginal deliveries. The incidence of traumatic rupture of the uterus has markedly decreased in the past 10 years.

The 18 spontaneous ruptures (not in previous cesarean section scars) occurred in patients who had tumultuous labors, in patients who had had previous difficult vaginal deliveries, in grand multiparas, in patients with babies that weighed more than 4,000 grams, and in patients who received fractional doses of Pitocin to induce or stimulate labor.

The use of fractional doses of Pitocin has been discontinued. We have not had a uterine rupture with Pitocin infusions, but their use is carefully controlled.

There have been 23 uterine ruptures of previous cesarean section scars. There were no maternal deaths in this group. Eleven had previous classical scars; 6 had low vertical; and 9 had low transverse. One had a scar from a hysterotomy for a hydatid mole. Of the 7 patients who had previous classical sections, 6 had complete ruptures and one had an incomplete rupture. Of the 15 who had had low cervical scars, only 2 had complete, and 13 had small, incomplete ruptures.

It seems that a rupture of a classical scar is more likely to be complete, and therefore, a more serious complication than rupture of a low cervical scar. Less than 0.5 per cent of the cesarean sections performed at the Margaret Hague Hospital are classical sections; yet classical section scars account for 32 per cent of the ruptures in this group, and 75 per cent of the complete catastrophic ruptures. It seems, therefore, that classical scars are more likely to rupture, and certainly, when they do rupture, it is often a more serious complication than the separation of a low cervical scar.

Now, as to the previous cesarean section—It has been a policy at the Margaret Hague for some time to give patients who have had a previous cesarean section a trial of labor. Dr. Robert Cosgrove reported a year ago that 35 per cent of the patients who have had previous cesarean sections are delivered by vagina at the Margaret Hague Hospital. In following this policy, we have not had a maternal death in rather a large experience. We have had 4 fetal deaths in this group, and I may say that 2 of those fetal deaths occurred before the thirty-sixth week of pregnancy. So, even if you were going to do elective cesarean sections at 38 weeks, you would not have been given an opportunity to do it in two of the cases.

It is possible that the other two fetal deaths might have been prevented by elective cesarean section at 38 weeks. But, elective cesarean section has an inherent fetal mortality of its own. Babies delivered by elective sections without labor have more and thicker intratracheal secretions than babies born per vaginam. They frequently have atelectasis. Then, it is very possible to mistake the date of confinement, and what we may think is the thirty-eighth week may be only the thirty-sixth or the thirty-fifth week.

I am sure that the thirty-five per cent of our patients who delivered vaginally after previous cesarean sections have, on the average, had more babies than the group which had repeat cesarean sections.

I realize that cesarean section is today a safe procedure, but any abdominal operation is not without its morbidity and adhesions which may be dangerous at a later date. By allowing patients with previous cesarean section and with no evidence of disproportion a trial of labor, we have been able to keep our cesarean section incidence down to 4.5 per cent—which we believe is high enough.

DR. A. CHARLES POSNER.—We agree with Dr. Meredith on two important points: first, the importance of exploring the uterus after even a simple operative delivery. Doing this will sometimes reveal a ruptured uterus, when you least expect it, and before any grave signs appear. Second, we believe that it is much safer to do a cesarean section electively than to wait for a ruptured uterus to occur. In the Harlem Hospital we ran two series of cases. In our first series of cases, reported in the *New York State Journal of Medicine* in 1951, we had 38,000 cases, with 14 ruptured uteri. There were 8 deaths. Our incidence was 1 in 2,724 cases. These constituted 13 per cent of the maternal deaths in this period. We decided that we would change our policy and increase our cesarean section incidence. The result was that we had more ruptured uteri. The incidence went up to 1 in 1,500, a figure similar to that reported by other observers. Of the 11 ruptured uteri in this group, however, 8 were incomplete and were found at the time of cesarean section. In this new group of 11 cases, we had one death, which occurred in a case of spontaneous rupture which was incomplete and accompanied by terrific hemorrhage.



## THE ASSOCIATION OF MATERNAL AND FETAL FACTORS WITH THE DEVELOPMENT OF CEREBRAL PALSY AND EPILEPSY\*†

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THE effects of the birth process and obstetrical procedures on the fetus and newborn infant have received a great deal of attention. Since 1843, when Little noted the association of abnormal parturition, difficult labors, premature birth, and asphyxia neonatorum with cerebral palsy, various neurological conditions of childhood, including mental retardation, epilepsy, and behavior problems, have been attributed to the birth process. There have been many differences of opinion as to the importance of such obstetrical factors as forceps and breech deliveries, analgesia and anesthesia in the etiology of these conditions. The investigators who thought that obstetrical factors played a role emphasized those that might produce mechanical injury to the brain of the fetus. A smaller group of investigators considered that the conditions which resulted in anoxia were of greater importance. Several investigators have also emphasized genetic causation.

Many of the differences of opinion merely reflected the difficulties that were inherent in the method of study. In studying cerebral palsy, for example, a basic problem resulted from the relatively low incidence of this group of conditions. This made it difficult for an investigator to obtain a sufficiently large number of cases to yield statistically reliable results. This also limited the number of obstetric factors that could be analyzed. Another obstacle in previous investigations was that of obtaining an adequate control group for comparison.

A rather important limitation resulted from the inability to separate obstetric factors that are associated with each other. For example, prematurity had been found to be associated with cerebral palsy in one study. In another, certain maternal complications were found to be associated. Since there exists a high correlation between prematurity and maternal complications, the question as to whether the basic relationship is with prematurity per se or with maternal complications which result in prematurity remained unanswered. This is a point of considerable interest since it would indicate whether or not a developmental defect of the fetus or the maternal environment were at fault. For, if prematurity is highly associated with cerebral palsy, it is conceivable that a fetal developmental defect was the principal cause of some of the premature births. On the other hand, if various compli-

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cations of pregnancy, without prematurity, were found to be associated, it would be difficult to believe that these complications were the result of the fetal defect. In these types of studies, it is necessary to dissociate the effects of as many of the obstetric factors as possible.

With this brief background, we would like to review a series of studies in which we have been engaged during the past few years. The first we would like to discuss is that concerning the association of the maternal and fetal factors with the development of cerebral palsy.

This study consisted of matching a record of events that had occurred during pregnancy and parturition with the diagnostic record of a cerebral palsied child. The crippled children's case register maintained by the New York State Department of Health for administering its crippled children's program was searched for those children with cerebral palsy who had been born between 1940 and 1947, and the birth register maintained by the Health Department's vital statistics office was searched for the birth certificates of these individuals. Both of these records were obtained for a group of 561 cerebral palsied children. Since 1940, in New York State (exclusive of New York City) the complications of pregnancy and labor, operative procedures, and birth weight have been voluntarily reported by physicians on the birth certificate, in addition to routine data such as age of mother and order of birth. By matching these two records it was possible to compare the cerebral palsied group with the births in the general population from which they were derived with regard to the various factors in which we were interested. Consideration was given only to single births, although it is of more than passing interest that 3.4 per cent of the cerebral palsied had been multiple births as compared with 1.2 per cent of the general population.

The results of this investigation have been previously reported in detail.<sup>1</sup> The following is a brief summary of these findings.

The mothers of about 38 per cent of the cerebral palsied group have had complicated pregnancies as compared with 21 per cent of mothers with live-born infants who had survived the first month of life. With regard to specific complications of pregnancy, the data suggested that those complications which resulted in higher stillbirth and neonatal death rates had a higher degree of association with cerebral palsy. In addition, complications such as placenta previa, malpresentations, nonpuerperal complications, and premature separation of the placenta—all of which are more prone to produce anoxia of the fetus—were more highly associated with cerebral palsy than dystocia and pelvic abnormalities which are more likely to produce mechanical trauma. The possibility that various obstetrical operative procedures such as forceps are related to cerebral palsy was not borne out after the association of complications with operative procedures was taken into consideration. Because of the small numbers remaining for final analysis, this does not eliminate the possibility of a relationship, but it would appear that, if operative procedures were as important as some investigators have thought, a greater association should have been present in our data. It was found that 22 per cent of the cerebral palsied group were prematurely born, as compared with 5 per cent of the total births in the population. This association with prematurity was

found to exist when prematurity resulted from complications and when the cause of prematurity was not known. An attempt was made to study the influence of maternal age and birth order. The only suggestive relationship was that the children of primiparas over 30 years of age may have a greater risk of developing cerebral palsy. A much larger series of cases would have to be analyzed before any definite conclusions concerning the effect of maternal age and birth order on the development of cerebral palsy could be reached, since such a study requires a breakdown of the cases into numerous categories. An additional finding of considerable interest was that 35 per cent more of the mothers of the cerebral palsied children had a history of one or more previous stillbirths or infant deaths than the total birth group. All of the differences noted are statistically significant. (Differences are considered statistically significant at probability levels of .05 or less.)

These findings appeared to indicate the presence of a definite relationship of various conditions associated with childbearing and the subsequent development of cerebral palsy. There also appears to exist a relationship between stillbirths, neonatal deaths, and cerebral palsy. The pattern of factors such as complications of pregnancy, prematurity, etc., which influence infant loss, seems to behave in a similar manner with regard to cerebral palsy. On the basis of these related patterns it was possible to postulate the existence of a *continuum of reproductive casualty* with a lethal component consisting of abortions, stillbirths, and neonatal deaths, and a sublethal component consisting of cerebral palsy and perhaps other related conditions.

Using this concept as a working hypothesis, we enlarged the scope of the inquiry to carry out similar studies of other neurological conditions such as epilepsy, mental deficiency, and behavior disorders of childhood. These conditions were studied because cerebral palsied children frequently suffer from convulsions and/or are frequently mentally defective. Behavior disorders were investigated since several investigators have thought that certain of these disorders are the result of brain injury. The study of epilepsy was carried out in Baltimore where the names of a group of 564 epileptic children were obtained from various clinics and institutions in the city. These epileptic children were those born in Baltimore since 1935, whose birth certificates were located in the files of the Baltimore City Health Department. Certain information, such as maternal age, birth order, place of birth, etc., was obtained from the birth certificate. As a control series of births with which the epilepsy cases could be compared, the next birth of an infant who had survived the neonatal period from the same place of birth, matched by race and maternal age group, was selected.

In those instances where the epileptic child and the matched control were born in a hospital, certain information concerning pregnancy and delivery was abstracted from the hospital record. The person obtaining this information from the hospital record was not informed which birth was that of a child with epilepsy or of a control child. The multiple births and those not born in a hospital were eliminated for the study of a majority of the obstetric factors, leaving 396 cases for analysis, of which 274 were white and 122 were nonwhite.

In comparing the epileptic group with the controls it was necessary to take into account the fact that a certain proportion—35 per cent of the white group and 16 per cent of the nonwhite group—had associated neurological defects such as mental deficiency, malformations, and cerebral palsy. Where size permitted, it was possible to look at these two groups separately.

A detailed description of the method of investigation and some of the results have been reported elsewhere.<sup>2, 3</sup> We would like, however, to summarize the results and present a few additional findings in this report.

The mothers of 27.7 per cent of the white epileptic children had had one or more complications of pregnancy as compared to 18.8 per cent of the controls; a difference which was statistically significant. In the nonwhite group 50.8 per cent of the mothers of the epileptics had one or more complications as compared to 43.4 per cent of controls. This difference was not statistically significant although it was in the same direction as the difference noted in the white group. These differences still existed even when the epilepsy cases were divided into those with and those without associated defects. It was also of interest that the mothers of epileptic children had had more multiple complications than the controls. Eight per cent of the white mothers of epileptic children had had two or more complications, as compared to 2.2 per cent of the controls, and 18.0 per cent of mothers of nonwhite epileptic children, as compared to 11.5 per cent of the controls. These results are presented in Table I. When the types of complications were examined, it was noted that toxemias and placental abnormalities, such as bleeding during pregnancy and placenta previa, were the ones that were more frequent among mothers of the epileptic children, a finding similar to that present in the case of cerebral palsy.

TABLE I. FREQUENCY OF VARIOUS ABNORMALITIES OF PRENATAL AND PARANATAL PERIODS AMONG EPILEPTIC CASES AND MATCHED CONTROLS, BY RACE

ABNORMALITY	WHITE				NONWHITE			
	EPILEPTIC		CONTROLS		EPILEPTIC		CONTROLS	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
With one or more maternal complications	76	27.7	51	18.8	60	49.2	53	43.5
With two or more maternal complications	22	8.0	6	2.2	22	18.0	14	11.5
Prematurity	34	12.9	10	3.8	19	15.3	15	12.3
Prematurity without maternal complications	15	5.5	7	2.6	8	6.6	6	4.9
Abnormal neonatal conditions	45	17.2	15	5.7	16	13.6	4	3.3
Abnormal neonatal conditions without prematurity or maternal complications	17	6.2	9	3.3	5	4.1	2	1.6
With one or more abnormalities of prenatal and paranatal periods	108	39.4	67	24.7	73	59.9	61	50.0
Total cases	274	--	271	--	122	--	122	--



The prevalence of other abnormal maternal and fetal factors among cases of epilepsy and controls is presented in Table I. We note that 12.9 per cent of the white epileptic children were premature as compared to 3.8 per cent of the controls. Among nonwhites, 15.3 per cent of the epileptic were premature as compared to 12.3 per cent of the controls. Because of the association of prematurity with complications, it was necessary to determine the frequency of prematurity in the absence of maternal complications among our groups. It was found that 5.5 per cent of births of white epileptic children were premature as compared to 2.6 per cent of controls, and among nonwhites 6.6 per cent of the epileptic were premature as compared to 4.9 per cent of the controls. Thus there was an association of prematurity with epilepsy even in the absence of maternal complications.

From the hospital records information was obtained concerning the status of the infant during the neonatal period. Neonatal abnormalities that were considered were convulsions, cyanosis, and asphyxia. The prevalence of these neonatal abnormalities among epileptics and controls is presented in Table I. We note that 5.7 per cent of white controls had neonatal abnormalities as compared to 17.2 per cent of epileptic cases, and 3.3 per cent of nonwhite controls as compared to 13.6 per cent of nonwhite cases. All of these differences are statistically significant.

In view of the fact that these neonatal abnormalities are associated with both prematurity and maternal complications, it was considered desirable to summarize these factors by disregarding the overlapping that occurs between these various conditions. Thus we would consider only those children who were exposed to one or more complications, prematurity without complications, and neonatal abnormalities without either maternal complications or prematurity. We would obtain an estimate of the total frequency of abnormal maternal and fetal factors in each of our groups. The results are presented in Table I. In the white group 39.4 per cent of epileptic children have been exposed to one or more of these abnormalities. When this group was divided into those with and those without associated defects, we found that 33.9 per cent of those without defects have one or more abnormalities as compared to 50.5 per cent of those with associated defects. These are to be compared with a 24.7 per cent prevalence among the controls. In the nonwhite group the prevalence of abnormalities is 59.9 per cent among the total epileptic children and 55.0 per cent among those without associated defects as compared to 50.0 per cent among controls. The differences in the white group are significant while those in the nonwhite group are not. It is not completely clear why differences in the nonwhites are not significant, although it must be granted that they are in the same direction. It is possible that nonsignificance results from the smaller number of cases among nonwhites. In addition, it might be a result of the smaller percentage of births in hospitals among nonwhites leading to some selection for complicated deliveries.

From hospital records it was possible to obtain information concerning the previous reproductive performance of the mother. If we consider abortions, stillbirths, neonatal deaths, and premature births as representing repro-

ductive casualties, we are then able to see whether the frequency of mothers who had one or more of these reproductive casualties was different among mothers of epileptic children than among mothers of controls. This was analyzed in terms of the ratio of the observed number of mothers with one or more previous reproductive casualties to the number expected if the percentage of mothers with one or more previous reproductive casualties in the control group had prevailed in the epileptic group. Thus if the observed/expected ratio was in excess of 100 per cent, this would mean that there was an excess of mothers with one or more previous reproductive casualties in the epileptic group. The results are presented in Table II. It was necessary to take birth order into account in the analysis. Considering the white and non-white groups as a whole, we note that 24 per cent more mothers of epileptic children had a history of one or more previous reproductive casualties than the mothers of the controls.

TABLE II. OBSERVED AND EXPECTED NUMBERS OF EPILEPTIC CASES WITH MATERNAL HISTORY OF PREVIOUS REPRODUCTIVE CASUALTIES BY BIRTH ORDER AND RACE

BIRTH ORDER	CONTROLS	EPILEPTIC CASES			
		TOTAL	R <sub>1+</sub>		
	PER CENT R <sub>1+</sub> *  R <sub>1+</sub>		OBSERVED NUMBERS	EXPECTED NUMBERS	OBSERVED EXPECTED RATIO AS PERCENTAGE
White.—					
2	11.9	73	14	8.7	161
3	25.7	45	17	11.6	147
4	50.0	15	8	7.5	107
5 and over	65.0	27	15	17.6	85
Nonwhite.—					
2	25.0	24	10	6.0	167
3	36.4	12	6	4.4	136
4	53.8	13	9	7.0	129
5 and over	71.4	22	18	15.7	115
Total	--	231	97	78.5	124

\* $R_{1+}$  = Maternal history of one or more previous reproductive casualties which includes abortion, stillbirths, neonatal deaths, and premature births.

We analyzed possible effects of length of labor, maternal age, birth order, and operative procedures. No differences were noted between the epileptic and control groups with regard to these factors.

The results appear to indicate that there exists a definite relationship of various maternal and fetal factors with the subsequent development of epilepsy. The pattern of association is similar to that found with cerebral palsy, stillbirths, and neonatal deaths, thereby indicating that epilepsy should be included in the hypothesized *continuum of reproductive casualty*.

A study with regard to mental deficiency has just been completed although all of the data have not yet been analyzed. Thus far the results follow a very similar pattern. Rogers<sup>4</sup> has just completed a study of the relationship of behavior disorders in childhood and the results are similar to those just reported. These studies will be reported at a later date. An over-all summary of the results of all of these studies is presented in Table III.

In addition to the over-all association of these conditions with maternal and fetal factors, it is important to note that those complications of pregnancy such as toxemias and the various types of bleeding are more highly associated with these conditions than the other complications. This would suggest that those complications which are more prone to produce nonmechanical injury, such as anoxia, to the fetal brain are more important factors than the complications which are related to mechanical trauma.

Another feature of interest is that the association is greater in the case of stillbirths and neonatal deaths than with other conditions and greater with cerebral palsy than with epilepsy. This would indicate that there exists a gradient of the degree of association which parallels what we might consider to be a gradient of severity of brain injury.

TABLE III. SUMMARY OF THE ASSOCIATION OF MATERNAL AND FETAL FACTORS WITH VARIOUS NEUROPSYCHIATRIC DISORDERS OF CHILDHOOD

NEURO- PSYCHIATRIC DISORDER	MATERNAL AND FETAL FACTORS					
	MATERNAL COMPLICATIONS OF PREGNANCY	PREMA- TURITY	NEONATAL CONDITION	OPERATIVE PROCEDURES	BIRTH ORDER AND MA- TERNAL AGE	PREVIOUS INFANT LOSS
Cerebral palsy	+	+	Not studied	-	+	+
Epilepsy	+	+	+	-	-	+
Mental deficiency	+	+		Not yet analyzed		
Behavior disorders	+	+	-	-	-	+

\* + = Definite association; +? = suggestive association; - = no association.

### Comment

Before discussing some of the implications of these results it is important to keep in mind the limitations on interpretation that are imposed by the type of material utilized. The question of a possible bias due to the selection of cases from case registers of a health department and from clinics must be borne in mind. Serious consideration must be given to the possible under-reporting of the maternal and fetal factors on both birth certificates and hospital records. An important limitation results from the fact that each of the neuropsychiatric conditions studied, cerebral palsy, epilepsy, mental deficiency, and behavior disorders, probably represents a heterogeneous group of conditions caused by multiple factors. Consequently, these results should not be interpreted as implying that maternal and fetal factors are the only etiological factors. Nonetheless, it appears that they are important factors and the quantitative estimate of their importance must await more refined methods of investigation.

The hypothesis of the *continuum of reproductive casualty* provides a conceptual framework for further research. It emphasizes the need for a longitudinal study starting as soon after conception as possible and continuing through prenatal and natal periods until the child is several years of age. Detailed information of events occurring during the prenatal, natal, and post-natal course could be obtained and related to the fetal deaths, malformations,

and other congenital diseases and disabilities. This type of study could be done either in the large obstetrical clinics or in the community as a whole. Most desirable would be a study of all or a sample of the pregnant women in the community, since this would eliminate the unavoidable bias involved in the selection of a population served by one or two hospitals.

There are some observations by other investigators that suggest that the concept of a *continuum* should be broadened to take into account the pre-conceptional period. Tietze, Guttmacher, and Rubin,<sup>5</sup> reporting on a study of unintentional abortions in 1,497 planned pregnancies, found that those patients who conceived within a six-month period had an abortion rate of 5.6 per cent, while among those who took longer than six months in which to conceive the rate was 12.3 per cent. The abortion rate also increased steadily with age in a pattern similar to that of other types of reproductive casualty such as stillbirths and neonatal deaths. More specific than this were the findings reported by Aaron, Levine, and Gitman<sup>6</sup> to this society last year. In studying 52 couples who had had two or more previous abortions, stillbirths, etc., they thought that the more constant etiological factors were abnormalities of the uterus and functionally defective endometrium.

In view of the fact that the pattern of association of maternal and fetal factors with the neuropsychiatric conditions studied is similar to that found with regard to infant loss, it appears that a fruitful area of research would be the investigation of the relationships of intrauterine abnormalities to maternal complications and to the effects of these abnormalities on the fetus.

During the past twenty-five years, one of the most brilliant chapters in the history of medicine and public health has been that concerning the remarkable reduction of maternal and infant deaths below levels that were expected. Obstetricians have played a major role in the realization of these results. These objectives were achieved principally by the application of therapeutic measures which have prevented mothers and infants from dying because of various morbid processes associated with pregnancy. The results of the studies which we have reported indicate that the maternal factors have other sequelae besides fatality. These nonfatal conditions in the fetus can be prevented only by the actual prevention of these morbid conditions in the mother. We must frankly admit that at the moment our knowledge of the factors causing placenta previa, premature separation of the placenta, toxemia, breech presentations, etc., is practically nil or at least not sufficient to allow us to prevent these conditions. Thus it appears that a reorientation in terms of a broadening of the scope and objectives of obstetrical practice and research is necessary so as to acquire the knowledge needed for the prevention of these sequelae of pregnancy and parturition.

### Summary

A study of the birth certificates of 561 cerebral palsied children born in Upper New York State between 1940 and 1947 showed that their mothers had significantly more complications of pregnancy and labor, prematurity, and previous infant loss than the population of births from which they were



derived. The pattern of the association of these factors with cerebral palsy was similar to that found with regard to stillbirths and neonatal deaths. This led to postulating the existence of a *continuum of reproductive casualty* composed of a lethal component consisting of abortions, stillbirths, and neonatal deaths and a sublethal component consisting of cerebral palsy and perhaps other related conditions.

Using this concept of a *continuum* as a working hypothesis, similar studies have been carried out in Baltimore with regard to epilepsy, mental deficiency, and behavior disorders of childhood. The results of the study of epileptic children are presented in detail while the results of the other studies are briefly summarized. The prenatal and paranatal records of mothers of 564 epileptic children born in Baltimore between 1935 and 1952 showed significantly more complications of pregnancy and delivery, prematurity and abnormal neonatal conditions than a similar number of matched controls. In addition, more mothers of the epileptic children had a history of previous reproductive casualties than the mothers of the controls. The fact that the pattern of association of these maternal and fetal factors with epilepsy, mental deficiency, and behavior disorders of childhood was similar to that found with regard to cerebral palsy indicates that these conditions should be included in the postulated *continuum*.

The importance of the concept of the *continuum* as providing a conceptual framework for obstetrical research and practice is discussed.

We would like to express our grateful appreciation to the directors and medical record librarians of the clinics and hospitals in Baltimore, to the staffs of the Statistical Section of the Baltimore City Health Department and the Maryland State Department of Mental Hygiene, without whose cooperation this study could not have been carried out. We would also like to acknowledge the assistance of Mrs. Frances Constantinou, R.N., Research Assistant in the Department of Public Health Administration, in obtaining the data upon which this report is based.

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## LUPUS ERYTHEMATOSUS AND PREGNANCY\*

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LUPUS erythematosus<sup>1, 2</sup> is a disease of unknown etiology. The pathologic lesions include edema, swelling of the ground substance between fibrils and fibrinoid degeneration of the collagenous connective tissue of the involved organs probably on the basis of derangement of the metabolism desoxyribonucleic acid. There is a predilection for the skin and the serous surfaces of the joints, pleura, heart, the vascular system, and gastrointestinal tract. The lymph nodes, the liver, the spleen, the kidneys, and the blood-forming elements are not infrequently affected.

The clinical manifestations vary with the extent of the pathologic processes and type of lupus erythematosus. The chronic discoid variety may be regional or widespread over the skin with erythematous scaling patches of various sizes and configurations which ultimately result in superficial skin atrophy and scar formation. A small percentage of these cases becomes systemic in character. The acute or subacute disseminated lupus erythematosus is a serious systemic disease which has a usual onset with malaise, irregular temperature elevation, weight loss, marked weakness, arthralgias, arthritis and Raynaud's phenomenon, and edema. Generalized adenopathy, hepatomegaly, splenomegaly, and various cardiac, renal, and cerebral manifestations occur frequently as the disease becomes more severe. The blood picture presents evidence of suppression of the hematopoietic system with leukopenia, anemia, and/or thrombocytopenia. Dermatologic manifestations may be completely absent or arise later in the course of the disease. The presence of lupus erythematosus cells makes the diagnosis certain. L-E cells are leukocytes containing ingested nuclear material. The antibody-like substance responsible for this phenomenon is present in the plasma of individuals affected by the systemic disease. The course is variable with remissions and exacerbations but usually terminates fatally. Only from 20 to 25 per cent of the patients remain alive for a period of five or more years.

In spite of the fact that lupus erythematosus occurs most frequently in women of childbearing age, very few cases complicated by pregnancy have appeared in the literature to date. The major texts and publications dealing with obstetrics give almost no reference to this serious malady or how it may be affected by pregnancy. The only significant comments regarding the influence and effect of pregnancy on lupus erythematosus appeared recently by Donaldson<sup>3</sup> and by Ellis and Bereston.<sup>4</sup> Donaldson found 15 cases in the

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literature and added 8 additional cases. Ellis and Bereston reported 3 cases and mentioned 99 cases which they were able to obtain by questioning 100 dermatologists. In this presentation it is our purpose to review and analyze carefully the cases which appeared in the literature to date and present 2 cases we had occasion to observe within the past two years.

Table I represents a summary of cases of acute disseminated lupus erythematosus and pregnancy found in the literature to date. Cases 1 and 2 were in a state of remission when pregnancy began and had an uneventful course. In Case 3 a therapeutic abortion was done with the onset of acute lupus erythematosus during pregnancy; the patient survived to have an uneventful pregnancy two years later. In cases 4 through 10 acute lupus erythematosus developed during pregnancy. Only 4 and 5 had a long-standing history of chronic discoid disease. Patient 4 developed acute dissemination early in pregnancy; she remained acutely ill and after a long period of hospitalization finally delivered a stillborn infant during the thirty-fourth week. She improved somewhat after delivery and eventually died six years later. Cases 5 through 9 developed acute lupus erythematosus during the latter part of gestation and succumbed to the disease. Only one of these five infants survived. Patient 10 was treated with cortisone and ACTH after the twenty-second week of gestation. The mother and baby did well.

Table II is a summary of cases of subacute disseminated lupus erythematosus and pregnancy. The data given are not as complete as in the acute group. Patient 1 was ill for 2 months before she became pregnant; she improved after a therapeutic abortion at 10 weeks' gestation. Patients 2 and 3 were in a quiescent stage of the disease but became subacutely ill during pregnancy. Both patients improved after expelling macerated stillborn fetuses at 6 months' gestation. Patients 4 and 5 improved during pregnancy and delivered normal infants.

Ten cases<sup>3, 5</sup> of chronic discoid lupus have been reported. Three of these became worse during pregnancy and improved after delivery, 2 improved during pregnancy and 5 were not affected. The 99 cases summarized by Ellis and Bereston<sup>4</sup> consisted of 56 acute, 13 subacute disseminated, and 30 chronic discoid cases of lupus erythematosus. In the acute group 14 patients died, 11 became worse, 17 improved, and 14 were unaffected by the pregnancy; there were 10 stillbirths and 6 neonatal deaths. In the subacute cases, 3 patients became worse, 3 were unaffected, and 7 improved. There were, however, 6 spontaneous abortions. The patients with chronic discoid disease were said not to be affected by pregnancy.

CASE 1 (also being reported elsewhere<sup>9</sup>).—*Subacute disseminated lupus erythematosus and pregnancy.* Mrs. G. B., 21 years old, gravida i, para 0, a white woman, was referred to us by an internist for obstetric care on March 14, 1953. He had been treating her for subacute disseminated lupus erythematosus since April 1, 1951. During the past year she had been hospitalized for acute exacerbations of the disease on three occasions; each time L-E cells were found. The last acute episode occurred in September, 1952. The patient had been treated with large doses of ACTH and cortisone varying from 45 to 125 mg. daily. At this time she was on a maintenance dose of 50 mg. of cortisone orally per day and 40 units of ACTH intramuscularly twice a week. Her past history other than that related to the lupus erythematosus was essentially negative. The menstrual history was normal. Her last menstrual period was Dec. 4, 1952, and the estimated date of confinement was Sept. 11, 1953. There were no abnormal physical findings. She was approximately three months pregnant. The pelvic measurements were adequate. Urinalysis and blood count were normal. The serologic test for syphilis was negative. Her blood was

TABLE I. PREGNANCY AND ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

CASE NO.	AGE	PARITY	GRAVITY	HISTORY OF ONSET IN RELATION TO CURRENT PREGNANCY	TREATMENT	COURSE DURING PREGNANCY	FINAL RESULT	
							MOTHER	INFANT
13	27	iii	iv	2 years	?	Quiescent	Good	Lived
	29	iv	v	4 years	?	Quiescent	Good	Lived
26	?	?	?	?	Testosterone and progesterone	Complete remission	Good	Lived
33	17	0	i	6th week	Therapeutic abortion 10th week	Acutely ill before abortion	Improved after abortion	
	19	i	ii	2 years	Symptomatic	Quiescent	Good	Lived
45	?	0	i	Chronic discoid lupus erythematosus 11 years. Acute dissemination 5th week	Prolonged hospitalization, palliative measures	Acutely ill	Slight improvement after delivery. Died 6 years later	Stillborn at 34th week
53	32	ii	iii	Chronic discoid lupus erythematosus 21 years. Dissemination at 5 months	ACTH	Acutely ill	Died 6 weeks post partum	Stillborn at 6th month
64	21	0	i	38th week	Large doses penicillin	Acutely ill	Died 3 weeks post partum	Died 2 weeks post partum
74	25	?	ii	6th month	Therapeutic abortion and oophorectomy	Acutely ill. Improved after abortion	Died 8 weeks later	Previa
84	21	i	iii	With this pregnancy	Symptomatic. ACTH last 24 hours	Acutely ill	Died 6th day post partum	Died at birth
95	?	?	i	38th week	Symptomatic	Acutely ill	Died 1 day post partum	Lived
1010	25	0	i	22nd week	Cortisone and ACTH	Improved during treatment	Good	Lived



type O, Rh positive. She was kept on a salt-free diet, multiple vitamins, and her maintenance dose of cortisone and ACTH. Her pregnancy was uncomplicated; she gained a total of 2 pounds and the blood pressure never rose above 140/90.

The membranes ruptured spontaneously on Sept. 2, 1953, nine days before her due date. The next day she went into labor and three hours after the onset was delivered, with a midline episiotomy and outlet forceps, of a living female infant that weighed 6 pounds, 7 ounces. The third stage and puerperium were uneventful. She was kept on the previously mentioned medications and has remained free of symptoms. The baby showed no signs of having lupus erythematosus. The mother is now again pregnant, is still taking daily 50 mg. cortisone by mouth, and is getting along satisfactorily.

CASE 2.—*Acute disseminated lupus erythematosus and pregnancy.* Mrs. A. T., 29 years old, para 0, gravida ii, was first seen on March 8, 1952. Her last menstrual period was Nov. 21, 1951, and the estimated date of confinement Aug. 28, 1952. There was a history of migratory joint pains of one year's duration. The menstrual history was not significant. One spontaneous abortion at 10 weeks' gestation had occurred about a year previously.

Physical examination disclosed a moderate pallor. The blood pressure was 140/80. Urinalysis was negative. On April 28, 1952, x-ray of the chest and the Kline test for syphilis were negative; the erythrocyte count was 2.52 million; hemoglobin 7.4 Gm.; leukocyte count 7,800. Urinalysis disclosed a 2 plus albumin, 30 to 40 white blood cells with clumping, and from 2 to 3 red blood cells per high-power field. The patient complained of fatigue. There was pitting edema of both feet and ankles. The blood pressure was 130/80. Medical consultation was obtained. No definite diagnosis was reached but a chronic glomerulonephritis was suspected. She was hospitalized between May 23 and May 29, 1952. The urine showed persistent albuminuria and white blood cells. The urea clearance was normal. A total of 1,500 c.c. of blood was given because of the severe anemia.

Hospitalization for the second time was necessary on June 17, 1952, because of severe dyspnea, orthopnea, generalized edema, and migratory joint pains. A severe anemia and albuminuria were again noted. The carbon dioxide combining power was 17 volumes per cent. Packed-cell transfusions, intravenous sodium lactate and oral sodium bicarbonate were given. The patient improved considerably and on June 23, 1952, spontaneous uneventful labor occurred with delivery of a male infant, weighing 500 grams, in very poor condition. The baby died the next day and autopsy revealed extensive interstitial hemorrhages of the cerebrum and cerebellum. Following delivery, the patient developed pain in the chest and the temperature rose to 101° F. X-ray revealed a pleuropericarditis. Rheumatic fever, collagen disease, and tuberculosis were considered. Antibiotics and other palliative measures were administered and the patient improved enough to go home on July 19, 1952, twenty-six days after delivery.

She was readmitted on July 25, 1952, because of vomiting, hemoptysis, and extreme weakness. The erythrocyte count at this time was 2.97 million, urea nitrogen 83.6 per cent; urea clearance 23 per cent of normal. X-ray revealed cardiac enlargement. On Aug. 1, 1952, she developed bilateral retinitis. The chest pain and dyspnea became worse. Her temperature rose to 102.4° F. At this time the entire case was reviewed. Because of involvement of the kidneys, lungs, and pericardium, and the history of joint pains, the possibility of lupus erythematosus was considered. The L-E phenomenon was positive. She remained in the hospital until Sept. 27, 1952, on cortisone therapy. She was discharged on 27.5 mg. cortisone daily to be followed in the medical clinic. The final admission was on Dec. 8, 1952, when she entered because of marked weakness. She grew progressively worse and died on Dec. 22, 1952. Autopsy findings revealed a chronic glomerulonephritis, cardiac hypertrophy, pericarditis, chronic pleuritis, interstitial pulmonary hemorrhage, abdominal ascites, cortical hyperplasia of the adrenals, and lupus erythematosus of the skin.

TABLE II. PREGNANCY AND SUBACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

CASE NO.	AGE	PAR-ITY	GRA-VID-ITY	HISTORY OF ONSET IN RELATION TO CURRENT PREGNANCY	TREATMENT	COURSE DURING PREGNANCY	FINAL RESULT	
							MOTHER	INFANT
1 <sup>s</sup>	22	i	ii	2 months before pregnancy	Therapeutic abortion of 10 weeks' gestation	Subacutely ill before abortion	Improved after abortion	
2 <sup>s</sup>	23	0	iii	18 months before pregnancy	Symptomatic	Subacutely ill. Toxemia. Spontaneous interruption	Improved 4-6 weeks post partum	Macerated stillborn 6 months' fetus
3 <sup>r</sup>	?	?	?	?	?	Subacutely ill. Toxemia. Spontaneous interruption	Unknown	Macerated stillborn 6 months' fetus
4 <sup>s</sup>	30+	?	iii	?	?	Improved	Good	Lived
5 <sup>6</sup>	?	?	?	?	Testosterone and progesterone	Improved	Good	Lived

### Comment

Ellis and Bereston<sup>4</sup> reported that pregnancy complicating acute lupus erythematosus resulted in a maternal mortality of 20 per cent and a fetal mortality of 30 per cent. In the subacute variety, there were no maternal deaths but the fetal losses were 46 per cent. In spite of these results they concluded that pregnancy does not affect the course of the disease and that therapeutic interruption of pregnancy should never be done. Donaldson<sup>5</sup> was of the same opinion even though he found that toxemia is more likely to occur in these patients. Table I demonstrates that 8 out of 10 patients became systemically ill during the current pregnancy. Five of these patients died early in the postpartum period. One patient remained chronically ill and died six years later. Only one infant survived among these 6 patients. The patient who had a therapeutic abortion at 6 weeks' gestation survived to have an uneventful pregnancy two years later; one patient got along well on cortisone and ACTH therapy. The acute case that we presented, though unrecognized, apparently was present in subacute form for at least one year before the patient became pregnant. The pregnancy no doubt was a great factor in her relatively early death. With the facts available we cannot help but agree with Crawford and Leeper<sup>5</sup> who stated that pregnancy is not a good omen for women with extensive lupus erythematosus.

Perhaps the introduction of ACTH and cortisone as therapeutic agents may aid in prolonging the life of young women affected by acute and subacute disseminated lupus erythematosus. Thus the obstetrician may be confronted with the care of a fair number of these victims during pregnancy. DeCosta and Abelman<sup>10</sup> have shown that cortisone and ACTH may be safely

used during pregnancy in the human being. They also suggested that the administration of cortisone may not interfere with ovulation and conception. Margulis and Hodgkinson<sup>11</sup> reported similar results. Our patient with subacute disseminated lupus erythematosus became pregnant while taking 45 to 125 mg. of cortisone daily for a period of nineteen months. The continuous oral daily use of 50 mg. of cortisone had no deleterious effect on conception and on the entire course of pregnancy and labor. Furthermore, it did not prevent her from becoming pregnant a second time within 6 to 8 weeks after termination of the first pregnancy. The first infant is developing normally. The second pregnancy now in the sixth month is progressing satisfactorily.

It is our impression that all patients when suspected of having any form of lupus erythematosus should be carefully observed during pregnancy and should be treated actively with all means at our command. The search for L-E cells may aid in the recognition of more cases earlier in the course of the disease. Any exacerbation or change from chronic discoid to subacute or acute dissemination cannot be taken lightly. After adequate medical and dermatologic consultation a therapeutic interruption of pregnancy may have to be considered. Actually, with our limited experience, we cannot speak authoritatively on this very serious problem. Careful evaluation and reporting of more cases by obstetricians will eventually give us more knowledge concerning the effect of pregnancy on this serious malady.

### Summary and Conclusions

1. A review of the literature and analysis of lupus erythematosus complicating pregnancy have been presented.
2. One case of subacute disseminated lupus and another of acute disseminated lupus erythematosus complicated by pregnancy observed by us during the past two years were summarized and discussed.
3. The available data disclosed a 20 to 60 per cent maternal and 30 to 50 per cent fetal mortality in the acute and a 46 per cent fetal mortality in the subacute disseminated lupus erythematosus complicated by pregnancy.
4. Patients with any form of lupus erythematosus may tolerate pregnancy well provided the disease is under control and in a quiescent state.
5. It is suggested that interruption of pregnancy may have to be considered in cases where the disease cannot be controlled medically.
6. The introduction of ACTH and cortisone as therapeutic agents may be of value in controlling the disease. More women may then live long enough to have uneventful pregnancies.
7. A plea is made for careful observation and reporting of lupus erythematosus complicated by pregnancy.

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### Discussion

DR. SAMUEL J. ZAKON.—Although chronic discoid lupus erythematosus with the familiar butterfly pattern of the skin of the face has been recognized for more than a century, the concept of acute disseminated lupus erythematosus as a severe systemic disease is of recent origin. Not with any sense of chauvinism but rather with a sense of pride and humility, I wish to state that this newer concept of acute disseminated lupus erythematosus is entirely American in origin and development. It was in 1904 that Osler's classic contribution (*American Journal of Medical Science*, vol. 127, 1904) on the subject of "The Visceral Complications of Erythema Multiforme" appeared.

In this paper Osler set forth the characteristic clinical features of disseminated lupus erythematosus as we know them now. He emphasized that the variable manifestations in the skin and in the internal organs were part of the same systemic disease. Osler recognized the insidious onset, the protracted course with remissions and relapses in some cases, and the tendency to hemorrhagic gastrointestinal and neurologic symptoms, and particularly the pathologic findings in the kidneys. It is indeed remarkable how little has been added to the clinical knowledge of this disease since Osler's classic paper appeared.

The next milestone in the history of our knowledge of lupus erythematosus appeared in 1924 in the form of a paper by Libman and Sacks which focused our attention on the widespread vascular damage that characterizes the pathologic picture of disseminated lupus erythematosus. Again in the past decade Klemperer and his associates in a series of papers made a great contribution to our understanding of the fundamental alterations in the tissues of disseminated lupus erythematosus—the widespread degenerative changes that occur throughout mesenchymal tissues in the form of fibrinoid degeneration of the collagen fibers and the mucinous nature of the extracellular ground substance. Then in 1948 Hargraves of the Mayo Clinic and Haserick of Cleveland observed a peculiar phenomenon that appeared in the bone marrow in patients with acute lupus erythematosus, this phenomenon consisting of agglutination of cells and phagocytosis of homogeneous material by leukocytes with the formation of so-called lupus erythematosus cells. Thus for the first time a laboratory diagnostic aid in acute lupus erythematosus was found and a new approach to the study of the pathogenesis of this severe disease.

Then came the discovery of the corticotropic hormones ACTH and cortisone and their beneficial effects in prolonging life and in producing lasting remissions in this dreadful disease, so that today Dr. Turner and his associates can present to you tonight their interesting case reports.

Up to the advent of corticotropic hormone therapy, pregnancy complicating systemic lupus erythematosus carried an extremely grave prognosis both to the mother and to the child. Few survived unless the uterus was emptied early. Now with the advent of our present better knowledge of lupus erythematosus and newer therapy. Dr. Turner and his associates could report at least one successful case. The obstetric literature on lupus erythematosus and the statistical studies that were reported on the effect of pregnancy on systemic lupus erythematosus often were influenced to a certain degree more by a theology than a scientific approach.

Patients with systemic lupus erythematosus, a grave malignant disease, should be advised not to become pregnant even in this age of ACTH and cortisone. One word of warning in spite of the L-E phenomenon—the diagnosis of lupus erythematosus is still to a large degree a clinical one and the most scrupulous observations of the patient and the careful evaluation of all findings are necessary for a correct diagnosis.

Thus in recent decades more understanding of the lupus erythematosus problem has been achieved than in the previous hundred years, even though the cause is still unknown.



## THE DETECTION OF RUPTURED MEMBRANES BY VAGINAL SMEAR\*†

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THE purpose of this paper is to present a new method for the detection of prematurely ruptured membranes, a problem which had been under investigation for many years. The importance of this complication of pregnancy lies in its association with an increase in maternal morbidity and fetal mortality. In 1929, Margaret Schulze<sup>1</sup> showed that, in 10 per cent of 600 patients, a latent period of more than twenty-four hours existed between the time of spontaneous rupture of the membranes and the time of onset of labor. She found a definite increase in fetal mortality because of infection, but no increase in maternal mortality. Maternal morbidity, however, was increased by approximately 20 per cent. The same observations were made by Morton and associates,<sup>2</sup> who showed that the latent period was longer than twenty-four hours if the rupture took place prior to the thirty-sixth week of pregnancy. More recently, Calkins<sup>3</sup> reviewed 7,000 consecutive deliveries and found that 1 of 7 patients had experienced premature rupture of the membranes. He also observed a lag period of more than twenty-four hours in 15 per cent of the group with ruptured membranes. When the lag period was present, fetal mortality was at least three times the average because of infection and/or prolapsed cord. This occurred despite the prophylactic use of penicillin in all patients. Maternal morbidity, however, was practically eliminated by the antibiotic.

Three major methods have been devised for the detection of ruptured membranes.<sup>4</sup> The first is based on the fact that the vagina, during pregnancy, has a pH between 4.5 and 5.5, whereas the pH of amniotic fluid is between 7.0 and 7.5. Thus, when the membranes are ruptured, the vaginal pH should be 6.0 or above. Nitrazine paper, litmus paper, and bromthymol blue have been used for this test.<sup>4, 5</sup> This method has the advantage of rapidity over the other techniques described. Its chief defect lies in its inability to detect a small quantity of freed amniotic fluid, too small to change the vaginal pH from acid to alkaline. Furthermore, the presence of blood in the vagina may give an alkaline reaction prior to the rupture of the membranes, resulting in a falsely positive test.

The second method is the microscopic demonstration of fat globules in the vaginal fluid.<sup>4</sup> It is not reliable prior to the thirty-second week of pregnancy because the quantity of vernix is frequently too small to permit free fat globules.

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†Presented at a meeting of the Obstetrical Society of Philadelphia in April, 1954.

The third method is the microscopic demonstration in vaginal smears of disintegrating squamous cells from the fetal skin.<sup>6</sup> This test demands someone trained in cytology, since disintegrating squamous epithelium from fetal skin and maternal vagina may be encountered in the smear, tending to confuse the uninitiated by their similar morphology. Moreover, characteristic fetal squamous cells are not consistently found in amniotic fluid prior to the beginning of the ninth lunar month, limiting the usefulness of the test.

The technique herein reported is a modification of the smear method, using the staining technique of Papanicolaou.<sup>7</sup>

Fig. 1.

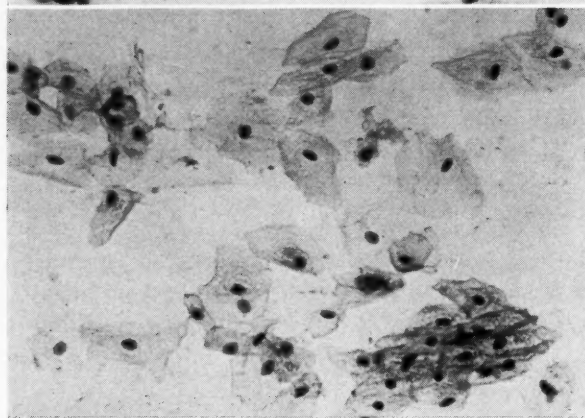
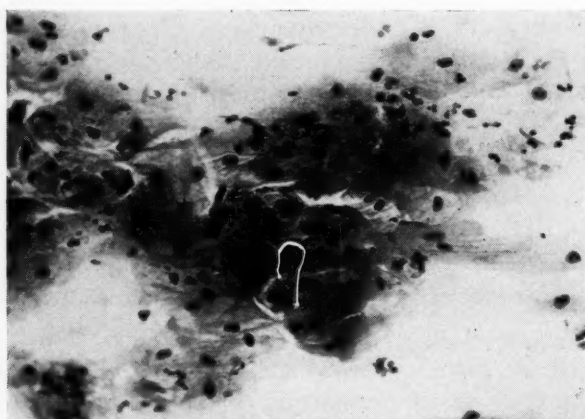


Fig. 2.

Fig. 1.—Prior to rupture of membranes.

Fig. 2.—One hour after rupture of membranes.

### Methods and Material

Fifty women in active labor were used as subjects for this study.\* Ten of the 50 patients were primiparous, and 40 multiparous. All of them gave a definite history and showed the physical findings of intact membranes. None had any type of vaginal infection.

A vaginal smear and pH reading were taken in each patient by the essayist during the admission examination. The smear was obtained by inserting

\*The patients were ward admissions to the Albert Einstein Medical Center, Southern Division.

a sterile glass tube into the vagina through which a sterile glass applicator was then introduced. The smear was taken as close as possible to the cervix. The vaginal smear slides were processed by the routine technique described by Papanicolaou. When clinically indicated, the patient's membranes were artificially ruptured and another smear taken, using the same technique. Smears were then repeated at regular intervals on those patients who had prolonged labors.

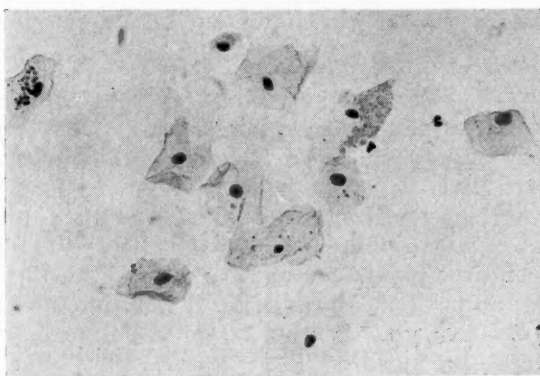


Fig. 3.

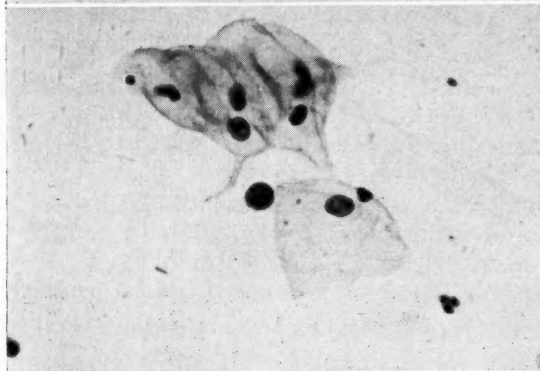


Fig. 4.

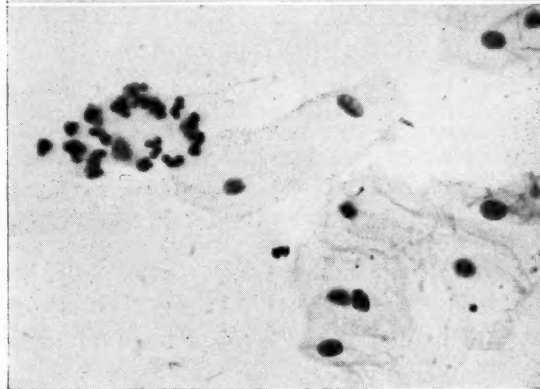


Fig. 5.

Fig. 3.—Three hours after rupture of membranes.

Fig. 4.—Six hours after rupture of membranes.

Fig. 5.—Eleven hours after rupture of membranes.

The vaginal pH was taken when the initial vaginal smear was made, using pHDrion controls—a pH indicator paper which gave an accuracy to two-tenths of a point. This reading was repeated at the time of the rupture of membranes. The pH findings were evaluated along with those of the vaginal smears.

### Results

The pH readings were distinctly acid as expected in 47 patients, ranging from 4.6 to 5.8. Following the rupture of the membranes, the pH values in the 47 varied from 6.1 to 7.4. In the remaining 3 patients, a pH of above 6.0 was obtained prior to the rupture of the membranes. A large quantity of blood was present in the vagina in each of these patients, however, and this undoubtedly accounted for the readings obtained.

The vaginal smears showed the following histologic characteristics:

*A. Prior to Rupture of the Membranes (Fig. 1).—*

1. Acidophilic (red) staining superficial vaginal and cervical squamous cells were diffuse and predominating, most frequently present in clusters. There were also some widely scattered basophilic (blue) superficial squamous cells, but they were definitely in the minority.

2. There were a few small cells with large nuclei that resembled intermediate vaginal and cervical cells. These were basophilic (blue stained).

3. The smears contained large numbers of leukocytes.

In this study, all 50 patients showed the typical histologic criteria prior to the rupture of the membranes. In 3 of these 50 patients, the squamous cells showed a basophilic stain, but they were still present in clusters. Furthermore, criteria 2 and 3 were present, making the slides easily identifiable.

*B. Immediately After Rupture of the Membranes (Fig. 2).—*

1. The squamous cells were predominantly basophilic (blue stained) and there were few clumps.

2. The cells resembling intermediate cells were now more prevalent, and were also basophilic (blue stained).

3. The smear had a "clean" appearance with few leukocytes.

The findings, following rupture, revealed an error in 1 of the 50 patients. Here, the diagnostic criteria were absent completely. It was obvious, however, that this smear was too thick and could not be properly stained.

*C. Several Hours After Rupture of the Membranes (Figs. 3, 4, and 5).—*

1. The intermediate cells were now predominating.

2. Only a small number of squamous cells were present.

The presence of leukocytes at this time is no longer of significance.

### Comment

It is often of considerable importance to determine quickly and accurately the status of the membranes during late pregnancy. Our present antibiotics and intravenous Pitocin induction could then be applied in indicated cases. To that end, this study was undertaken.

Vaginal pH determinations were obtained prior to and following the artificial rupture of the membranes. While this method has the advantage of rapidity over any other technique yet described, the results are not accurate.

Histologic criteria have been established whereby rupture of the membranes may be definitely determined by vaginal smear. The staining technique takes but two hours, and the slide may then be read immediately. (It is interesting to note that the squamous cells stain red when the vaginal pH is acid, and blue when this pH is alkaline.) The outer layer of squamous cells is probably washed away by the amniotic fluid, permitting the intermediate



cells to be present in greater numbers, and to predominate several hours later. The absence of leukocytes is probably caused by the cleansing of the vagina by the amniotic fluid.

This study is offered only as an introduction to this subject. To make it valid, smears must be done on more patients, particularly problem cases, and checked against the patient's clinical course. This work is in progress.

### Summary

1. Fifty women in labor were studied in reference to membrane status by means of determination of vaginal pH and vaginal cytology.
2. The pH readings showed an error in 3 of the 50 patients.
3. The vaginal smear technique was uniformly reliable in 49 of the 50 patients. The single error is attributed to a badly taken, too thick smear.

I am deeply indebted to Drs. S. Leon Israel, Albert I. Rubenstone, and David R. Meranze for their encouragement and assistance.

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### Discussion

DR. S. LEON ISRAEL.—Dr. Goldfine in his prize-winning paper has chosen an apt example of the unsolved problems in our specialty, the importance of which he emphasized in his introduction by reminding us of the threat present in the lag period. Reviewing critically the current methods for recognition of membrane rupture, Dr. Goldfine pointed out the vulnerable areas of error in each. In fact, his own correlation with the pH-reading technique indicated that blood in the vagina, a likely contaminant in labor, invalidates the accuracy of such estimates.

There seems little doubt from the clear-cut alterations noted in Dr. Goldfine's illustrations that Papanicolaou smears define changes following membrane rupture which indicate alkalinization and cleansing of the vagina. The latter, washing away of leukocytes, is readily acceptable by reason of the downward flow of the fluid over the vaginal surface. The change from acidophilic to basophilic staining in the superficial squamous cells after rupture of the membranes, a phenomenon which Dr. Goldfine attributes to the effect of the alkaline amniotic fluid, is an arresting observation. It is a provocative suggestion that fluid resting on the surface of the vagina may be responsible for the staining quality of vaginal epithelium garnered by smear. One usually regards the staining quality of the vaginal cells as being influenced chiefly by the circulating level of estrogen. Thus, during the ovarian cycle, acidophilic squamæ predominate at the height of the estrogen phase, only to give way to basophilic squamæ during the postovulatory phase. This has been ascribed to changes in the internal milieu of the cells, related in some way to the rise and fall of estrogen level and not to alkalinity of the vaginal surface fluid. The vagina remains acid throughout the reproductive years, its pH fluctuating between 4 and 5. At no time in the cycle, even at the height of the postovulatory phase when basophilic staining characterizes the vaginal smear, is the vagina alkaline. As a matter of fact,

three members of this Society—Rakoff, Feo, and Goldstein—reported to us ten years ago in their invaluable study of vaginal acidity that the gradient of pH change during the cycle never exceeds 0.6 degree. Therefore, the suggestion of Dr. Goldfine that the alkaline amniotic fluid causes the customarily acidophilic vaginal cells to become basophilic makes me wonder whether or not the slight change toward being less acid in the postovulatory phase may not be sufficient to be responsible for the cyclic alteration of staining quality in the vaginal smear.

Returning to the value of Dr. Goldfine's test for rupture of the amniotic sac may I state that he has demonstrated a simple, seemingly effective method of detection. He would be the last to be categorical on the basis of 50 patients, and I urge him to carry his study forward to a larger group of parturients.

## CERVICAL DYSTOCIA VERSUS UTERINE INERTIA

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FIFTY-NINE cases of cervical dystocia at the Southern Baptist Hospital from Jan. 1, 1944, to Jan. 1, 1954, will be analyzed herein. Undoubtedly there are more cases in which unusual rigidity of the cervix caused prolongation of labor but these are the only ones for which this diagnosis is recorded. No effort was made to study the charts of patients designated as "elderly primiparas," although it is an axiom of obstetrics that the primigravida over 35 years of age and at term frequently has a prolonged labor. One of the factors in this prolongation is an unyielding cervix but another equally important factor is uterine inertia characterized by infrequent contractions of poor quality and short duration. Moreover, these patients as a group seem less able to tolerate the pain attending these contractions. In addition, the added factors of prolonged sterility and "high priority" babies frequently associated make these patients more liable to section without labor.

It is not the purpose of this study to argue the pros and cons of performing cesarean sections on elderly primigravidas but to emphasize that there is frequently associated with an alleged unyielding cervix a definite lack of normal labor mechanism. It behooves many of us to recognize this fact and to make efforts to correct the uterine dystocia and forget the cervix, at least temporarily.

### *Age Incidence.—*

In this series there were 13 multiparas (6 para i, 4 para ii, one para iii, and 2 para iv) and 46 primiparas. The average age of the multiparas was 32.4 years, 4.6 years over that of the primiparas, which is as would be expected. The youngest mother in the series was 16 and the oldest 42. Fourteen patients (23.7 per cent) were 35 years old and older (9 of whom were primiparas), 24 were 30 years old and older, 4 were under 21, and the remaining 31 (52.5 per cent) were 21 through 29 years of age.

### *Cauterizations and Surgery.—*

Five of the patients had had previous cervical surgery, 3 had had cervical cauterization, and one had had previous rectal surgery which figured in the indication for section but of course had nothing to do with the progress of labor itself. One patient who had had surgery was delivered by midforceps after a twenty-hour labor, two were sectioned after trial labors of eight and nine hours, respectively, and one was sectioned after a failed medical induction. One 37-year-old para iv with a previous Sturmdorf procedure had a cesarean section-hysterectomy following an ineffectual fourteen-hour trial of labor. Two of those who had had cauterizations delivered vaginally, one with a nineteen-hour labor and the other with a thirty-eight-hour labor. In addition there was one patient delivered by cesarean section without labor because of two previous

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labors complicated by cervical dystocia and postpartum hemorrhage. There was another patient with a history of a cervical laceration with her previous delivery. She was sectioned after a medically induced eight-hour labor.

It is not our purpose to analyze critically the handling of each case, merely to present en masse all the data contained on the charts with brief discussion where it seems appropriate.

*Type of Delivery.*—

There were three sections performed without labor, one on a 42-year-old primipara, one on a doctor's wife, aged 22, with "congenital stenosis of the cervix," also a primipara, and one because of a history of dystocic labors. Three more patients were sectioned after failure of medical inductions, two with two attempts each at medical induction. The average length of labor of the remaining 37 patients delivered by section was 23.9 hours, for the vaginally delivered patients 24.0 hours. There were 43 sections done in the entire group, 6 midforceps, 8 low forceps, and 2 spontaneous deliveries. The section rate was 72.88 per cent.

*Onset of Labor.*—

Forty-four patients went into labor spontaneously, 10 had medical inductions (3 of which failed), one had a catheter induction, and one a medical induction plus amniotomy. The 3 failed medical inductions ended in cesarean sections. Three patients in whom labor was induced delivered vaginally after labors of twenty-nine, thirty-five, and forty-two and one-half hours, respectively. Six terminated in section with labors ranging from six to thirty-three hours. Fifteen patients received oxytocics during labor, three of whom also had medical inductions. These supplements ranged from  $\frac{1}{2}$  minim of Pitocin or 5 c.c. of Calgluquine to Pitocin infusions. Six of the 15 were delivered vaginally and 9 were sectioned. The section rate in the group with supplemented labors was 60 per cent.

Concerning fetal maturity, 48 patients were within two weeks of term. Of the 11 not strictly "at term" according to menstrual history calculation, 2 were four weeks late, 4 were three weeks late, 2 were two and one-half weeks late, one three weeks early, one four weeks early, and one six weeks from term. Labor was induced in 6 of the 8 overdue patients, all of whom were sectioned, one of the induction attempts having been fruitless.

*Presentation.*—

There were 4 patients with breech presentation in the series, all delivered by cesarean section after labors of from fourteen to forty-eight hours. The remaining 55 presentations were cephalic, 18 of these in one of the posterior positions. There was one face presentation. The rest were either in transverse or anterior positions. No attempt was made to analyze the transverse positions for two reasons, one, that in no case was it mentioned that a transverse position played any role in prolonging labor, and the other that, as is well known, frequently in normal labors the head descends well into the birth canal as a transverse before rotating to the anterior for delivery. According to Jacobs,<sup>1</sup> by x-ray evidence of patients at term and before labor, two-thirds of the heads are in one of the transverse positions.

There was one mentoposterior position. This patient was a 40-year-old para iii whose youngest child was 16 years of age. She was sectioned after an irregular fourteen-hour labor because of an "unfavorable cervix." Four of the posteriors were delivered vaginally, all by midforceps, with the average length of the labors twenty-seven and three-quarter hours. Three patients had forceps rotations and one a manual rotation.



*Disproportion.*—

The average weight of the babies in the entire series was 7 pounds, 7 ounces, which is about the weight of the average newborn infant. Six were under 6 pounds at birth and 10 weighed over 8½ pounds, with extremes of 4 pounds, 5 ounces, and 10 pounds, 1 ounce. The average weight of the 16 vaginally delivered babies was 7 pounds, 1 ounce, of the 43 babies born by section, 7 pounds, 11 ounces. In only 11 cases was there any stated cephalopelvic disproportion which ranged from 50 to 450 c.c. In all cases this discrepancy was at the midpelvis. In 2 cases the amount of volumetric disparity was not stated, one pelvis being diagnosed radiographically as anthropoid. In another case the clinical impression was that the pelvis was malformed although radiologically it appeared gynecoid with a 60 c.c. discrepancy. Seven of the group with disproportion were sectioned and 4 delivered vaginally.

*Status of Cervix.*—

On 30 charts of the 43 patients who were sectioned there were notations regarding the state of dilation of the cervix immediately prior to section. Of course, 6 of these 43 had no labor. In 22 cases the dilation was stated at less than 5 cm., and in 8 cases it was 5 cm. or more. Various descriptive terms were applied to these cervixes, such as *thick, rubbery, unripe, firm, fibrotic, rigid, hard, edematous*, and "bridged with scar tissue." These terms correspond closely to those employed in Sackett's<sup>2</sup> paper.

*Quality of Labor.*—

Twenty-five cases were complicated by uterine inertia. One case was diagnosed as "dystocia dystrophy syndrome" and one patient was noted to have a short stubby build. Several remarks were also applied to the labors, including "piddling" pains, irregular pains, poor or faulty mechanism, and "satisfactory labor did not develop." Eighteen of these 25 ended in section after labors ranging from six and one-half to forty-eight hours, the average being 29.7 hours. Five were delivered by low forceps, 2 having had fifteen-hour labors and the others thirty-five, thirty-six, and thirty-eight hours, respectively. One was delivered by midforceps after a medically induced forty-two and one-half hour labor and one spontaneously after nineteen hours. This last patient was a short, stubby, para ii, who had primary inertia and had had a previous cauterization. She received Pitocin booster injections during labor and delivered a 7 pound, 15 ounce baby following a manual dilation of the cervix. One of the cases which terminated in section had a catheter induction with a thirty-three-hour "piddling" labor, saddle-block anesthesia during labor, and one Dührssen's incision and an episiotomy. The baby, who was in a left occipitoposterior position, weighed 6 pounds, 5 ounces. The mother had an afebrile postpartum course.

Two charts mentioned a manual dilation of the cervix and 2 admitted to cervical lacerations. Other stated complications included one case of pre-eclampsia, one postpartum hemorrhage, one case of secondary anemia and paroxysmal tachycardia, one of fetal distress and maternal exhaustion, one of partial abruptio placentae, and 3 cases of postoperative ileus.

**Case Report**

This was a 16-year-old primigravida whose estimated date of confinement was Dec. 8, 1953. Her prenatal course was uneventful and she gave no history of treatment of cervical disorders. The membranes ruptured prematurely at 11 P.M. on Nov. 8, 1953, and labor began spontaneously at 3 A.M. on Nov. 9, 1953. Eight hours later cervical dilation had reached 4 cm. with the presenting part 1 cm. below the ischial spines, but after three more hours, in

spite of a good mechanism of labor, no further dilation had occurred. Pelvicephalograms during labor revealed a 150 c.c. midplane cephalopelvic disparity, by the Ball technique. At 2:20 P.M., eleven hours after the onset of labor, vaginal examination was performed and revealed a "hard, fibrous ring" at the external os. The main body of the cervix was described as "soft and 90 per cent effaced." The ring was torn by spreading the fingers inserted in the os. By virtue of the forceful labor mechanism, the cervix became completely dilated and delivery of a 4 pound, 15 ounce, baby was accomplished at 2:50 P.M. by low forceps and episiotomy under pudendal block anesthesia supplemented with ethylene. A 1½ cm. cervical laceration was sustained which was repaired. No oxytocics were employed before delivery. The postpartum course for both mother and baby was uneventful.

### Comment

Four patients in this series received two anesthetics, once during labor and once for delivery. These intrapartum agents were saddle blocks. One of these patients delivered vaginally by midforceps (left occipitoanterior) after a twenty-hour labor. The others were sectioned after twelve, twenty-nine, and thirty-three hours of labor. Why these agents were given before the patient was ready to deliver was stated in only one case—"to slow labor followed by cesarean section." The reason for their use on the other three patients is unknown. Whether it was to give the patient some brief respite in the hope that a good labor would ensue, or to relax the cervix in some obscure fashion (Schwarz and Woolf<sup>3</sup>), or to allay the patient's misery while preparations were made for section, or whether a mistake was made in judging the imminence of delivery, cannot be stated.

Seven of the 37 patients who were sectioned after labor displayed postoperative morbidity. There was one morbid patient among the 16 who had vaginal deliveries. The 18.9 per cent section morbidity is not out of keeping with the usual rate in nonelective sections. The liberal use of antibiotics during labor and post partum no doubt helped keep this incidence low. Blood transfusions and parenteral fluids also helped minimize pyrexia from dehydration and made for smoother postoperative courses and quicker recoveries.

There was one stillbirth in the series which was due to erythroblastosis. There were no maternal deaths and no infants died in the neonatal period. It is not to be assumed, however, that the eventual outcome of the babies was normal. The morbidity attending prolonged labors and midforceps procedures is well known.

The fact that there was only one postpartum hemorrhage seems rather remarkable inasmuch as an inert uterus tends to remain so post partum, and a uterus worn out by a long labor tends to lack the desired tonus after delivery.

The similarity in the average length of the labors terminating in section and in vaginal delivery may be deceptive without critical study. In the first place this is a small series so that not very sweeping conclusions can be drawn. In the second place, with 25 cases of inertia out of 53 which actually developed labor of sorts, it may be difficult to ascertain when true labor contractions developed following the prelabor mechanism, painful Braxton Hicks contractions, or "Pit" pains. Further, and most important, the length of labor of the patient who has a vaginal delivery is self-determined while that of the sectioned

patient is determined by the patience or lack of patience of the obstetrician, barring emergent complications. The shortest labor ending in vaginal delivery was eleven hours, fifty minutes, the longest forty-two and one-half hours, whereas one patient was sectioned after only six and one-half hours of labor, four and one-half hours of which were described as "hard." This was a 23-year-old primigravida with a right occipitoposterior position and a 7 pound, 5 ounce baby. The cervix was 3 cm. dilated at the time of section and no disproportion was mentioned. The longest labor ending in section was seventy-two hours. This labor began spontaneously and produced a 5 pound, 4 ounce baby three weeks early in a right occipitoposterior position. Undoubtedly, with a little more patience in some of these cases, the average length of labor in the sectioned group would have exceeded that of the vaginally delivered group. And some few of these would likely have delivered vaginally and then have been entered on the other side of the ledger. Lacking further information regarding fetal distress and maternal exhaustion (the latter unlikely in a six and one-half hour labor) one can but conclude that the chief claim to fame in some of these cases was perhaps the haste of the attending physician. The attributes of patience and impetuosity do not seem to be the exclusive property of any one group of accoucheurs, the specialists and general practitioners having similar shares of each. In only one case of vaginal delivery did the obstetrician indicate that he wished he had done a cesarean section.

An interesting fact which came to light during this study is that the earlier cases in the series seemed to have, as a group, longer labors. This may indicate that the accoucheurs are becoming less patient, or more adept at detecting which patients will or will not deliver safely before the passage of a great deal of time. Or it may indicate that they are becoming more proficient at judging the onset of true labor. The possibility must be considered that, for the extremely long labors, true labor did not actually exist for the entire length of time stated. One must also question the actual presence of cervical dystocia and/or uterine inertia among such short labors as twelve or fifteen hours. Here we must give the chronicler the benefit of the doubt, to the effect that he felt the cervix and determined it to be rigid, fibrous, or the like. Or that he attended the labor and witnessed the waning of a previously good mechanism.

It is suggested that more intravenous fluids during labor, a well-timed rest with heavy sedation, followed by the judicious use of Pitocin in cases similar to some of these, might result in a higher incidence of successful vaginal deliveries. True cervical dystocia without accompanying inertia is another thing again. For those cervixes which fail to dilate in spite of powerful eutocic contractions and which are discovered on vaginal examination to be pathologically rigid, cesarean section seems the only logical way out. For those which dilate partially, but over a long period of time, a routine of management similar to that employed in secondary inertia might be utilized to advantage. Hastening of dilation can be effectively and safely evoked by making multiple closely spaced nicks with the scissors for a depth of 1 to 2 mm. through the cervical mucosa in the region of the unyielding ring, provided the dilation is more than



6 cm. And for greater dilations, with the head low in the birth canal and under the most ideal of circumstances in regard to anesthesia, assistance, asepsis, and available blood for transfusion (not to overlook adeptness of the obstetrician), Dührssen's incisions are not to be forgotten.

Due mention should be made of the condition known as *conglutinatio orificii externi*. This situation occurs usually in multiparas and is characterized by failure of the cervix to dilate, also in spite of effective labor contractions. The cervix becomes completely effaced but dilates little or not at all. A thin fibrous band is responsible for the condition, which, when ruptured with the examining finger, or with a hemostat inserted under direct visualization through a pinpoint os, permits the cervix to dilate rapidly and completely and usually without becoming lacerated. A similar condition may obtain at greater dilations, for which the same treatment is effective, but which by definition, is not a true conglutination. In all probability many cases of sudden delivery in bed, following examinations which reveal little or no cervical dilation, belong to these latter categories. The examination likely supplies the little additional force required to rupture the fibrous bands.

### Conclusions

Several valid conclusions, I believe, can be reached from this study.

The first is that, in many cases, adequate information is not available for proper critical analysis. At times it is of great value for personal reactions as well as pertinent facts to be recorded, especially in cases with less clear-cut and classical attributes.

The second is that some reports give the impression the attending physician is trying to mislead either himself, his consultant, or whoever happens to bring the case under close scrutiny. Certainly, in a gravida v, para ii, abortus ii, "habitual abortion" as an indication for section is pretty doubtful.

The third is that many cases diagnosed as cervical dystocia actually are uterine inertia and little else. The failure of the cervix to dilate may mean that the patient is not really in labor. Periodic painful hardening of the uterus at term does not necessarily signify labor, especially in the presence of Pitocin injections. We have all seen medical inductions fail, and the patient go home only to return, frequently in less than a week, in spontaneous labor. Even two failed medical inductions should not lead one to throw up his hands in despair, provided the patient's condition does not demand immediate emptying of the uterus. It is entirely possible that some of the unyielding cervixes in the inductions of this series were not pathologically rigid, but merely "not ripe."

### Summary

1. Fifty-nine cases of cervical dystocia are presented by combination and analysis of the data.
2. Three cases followed cervical cauterization, five followed previous surgery on the cervix, and one followed a known previous laceration. It is possible that



even untreated chronic cervicitis may cause sufficient fibrosis to impede normal dilation during labor.

3. Forty-three patients were delivered by cesarean section and sixteen vaginally. Six sections were done without labor, three following failure of induction attempts.

4. There were fifty-five cephalic presentations and four breech. Varying degrees of cephalopelvic disproportion were present in eleven cases. There were eighteen occipitoposterior positions and one mentoposterior. The fetal weights were about average, the section babies weighing an average of 10 ounces more than the vaginally delivered babies.

5. The average length of labor of the patients delivered by cesarean section and those delivered per vaginam were about the same. With a little more patience in some of the cases of the former group, vaginal delivery could probably have been successfully accomplished.

6. Twenty-five patients were noted to have uterine inertia. It is suggested that in some of these cases this was the principal factor rather than cervical dystocia in the prolongation of labor, and with further attention to the inertia, there might have been more successful vaginal deliveries. Failure of good labor to develop from an induction attempt does not mean that the patient will never go into labor or that the cervix will not dilate properly.

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## ENDOGENOUS CREATININE CLEARANCE AS A MEASURE OF RENAL FUNCTION IN NORMAL AND TOXEMIC PREGNANCIES\*

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SINCE proteinuria was recognized as a common occurrence in toxemias of pregnancy, extensive research has been directed toward finding some renal function test which would shed light on the etiology of pre-eclampsia and eclampsia, and permit earlier detection and a more satisfactory means of evaluating the severity, progression, and prognosis of the disease.

Many tests commonly used in assessing impairment of renal function have proved to be of little value in the management of the toxemia patient because they either do not demonstrate abnormality until late in the disease or are inconsistent with the clinical evidence of its severity. As stated by Chesley,<sup>1</sup> "No renal function test has been developed which is of any value in assessing the severity and progression of preeclampsia."

Simultaneous urea and uric acid clearances have proved to be of some value in the differential diagnosis of the toxemias of pregnancy although such tests are not entirely specific.<sup>2</sup> Also, conventional renal function tests may be of value in assessing the more severe degrees of residual renal damage but often do not reflect the effects of future pregnancies.

Most measures of kidney function involve clearance studies in which varying proportions of the test substances prove to be partially excreted or partially reabsorbed by the tubules. The first accurate measure of glomerular filtration followed introduction by Smith and his associates<sup>3</sup> of the use of inulin, a substance which is completely and freely filterable at the glomerulus and is not reabsorbed by the tubules. Unfortunately, the inulin clearance is largely confined to experimental use and is of practically no value to the clinician since such a test involves hospitalization, continuous intravenous infusion, limitation of the testing to a relatively short period of time under unphysiologic conditions, and many other technical difficulties.

Attempts were made to measure glomerular filtration using exogenous creatinine<sup>4</sup> but subsequently it was demonstrated that some of the ingested creatinine was secreted by the tubules and, therefore, was an inaccurate reflection of glomerular filtration.<sup>5, 6, 7</sup> Too, Camara and associates<sup>8</sup> clearly demonstrated the effect of preformed creatinine in meat on the creatinine clearance. By doing simultaneous *endogenous* creatinine and inulin clearances, however, Brod and Sirota,<sup>9</sup> Miller and Winkler,<sup>5</sup> and Steinitz and Turkänd<sup>10</sup> observed that the inulin clearance/creatinine clearance ratio averaged 1.0 in normal people. Such studies indicate that for practical purposes endogenous creatinine is neither

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reabsorbed nor excreted by the renal tubule cells and that the endogenous creatinine clearance is a good clinical method for the estimation of the glomerular filtration rate.

Although there is some excretion of endogenous creatinine by the tubules in patients with severe renal disease, as pointed out by Camara and his co-workers, this potential error is offset for the most part by the use of the Bonsnes and Taussky<sup>13</sup> method of measuring serum creatinine since this method determines total chromogen. The higher proportion of noncreatinine chromogen in patients with severe renal disease introduces a second error, but the direction of the two errors is such that they tend to offset each other. This results in only slightly higher values with endogenous creatinine clearances as compared with simultaneous inulin clearances in patients with severe renal disease.<sup>8</sup> Brod and Sirota observed a difference of at least 10 per cent when the filtration rate was reduced to one-third of normal but such a discrepancy only in the presence of severe renal disease does not detract from the clinical usefulness of the endogenous creatinine clearance test.

The hourly urea clearance test has been in use since 1928<sup>11</sup> and has proved to be of clinical value in assessing renal function in toxemias of pregnancy. It does not meet several desirable requirements, however. As performed in the average hospital, the urea clearance test is often subject to gross errors, usually due to inaccurate hourly collections of urine. As indicated by Camara, a few minutes' error in one 60 minute collection combined with retention of a few milliliters of urine in the bladder often produces an error greater than 10 per cent. The same inaccuracies in the 24 hour endogenous creatinine clearance test produce an error of less than 1 per cent.<sup>8</sup> In addition, the urea clearance does not measure a single phase of renal function. This test gives no precise information about the glomerular filtration rate because of wide variation in tubular reabsorption and excretion of urea. However, reduction of the urea clearance commonly observed in pre-eclampsia and eclampsia is probably due more to a decrease in glomerular filtration than to change in tubular function.

### Study Groups

In view of the preceding observations, this study was undertaken to assess the clinical value of the 24 hour endogenous creatinine clearance test in obstetrics. The patients studied were divided into three groups: (1) control series of normal pregnant patients, (2) those pregnant patients with hypertension, diabetes mellitus, chronic renal disease, molar pregnancies, or a history of previous pre-eclampsia or eclampsia, and (3) those not in Group 2 who developed pre-eclampsia-eclampsia.

### Methods

Each patient on whom part of the study was carried out on an outpatient basis was carefully instructed in the collection of a 24 hour urine specimen. For two days before and during the urine collection, the patients were on a meat-free diet. The urine specimens were collected through an indwelling catheter from those patients who were hospitalized with toxemias of pregnancy. In the latter group, in several instances the initial specimen was obtained without a preceding meat-free diet. Because there is practically no fluctuation in the

blood serum creatinine during a 24 hour period following such dietary preparation, a single specimen of 10 c.c. of blood was obtained from each patient during or shortly following the 24 hour collection of urine.

Quantitative protein and creatinine determinations were done on the same urine and blood specimens. The total serum proteins were determined by utilizing the modified Weichselbaum biuret reagent. Quantitative 24 hour urinary protein excretions were determined by an extension of the standard biuret method.<sup>12</sup>

Bonsnes and Taussky's<sup>13</sup> modification of the Folin method was utilized in blood serum and urinary creatinine determinations. The 24 hour clearance was calculated by dividing the 24 hour urinary excretion of creatinine in milligrams by the concentration in the serum expressed in milligrams per liter.

The clearances were then corrected and reduced to per cent in order to standardize the results. After the dietary preparation utilized in this series of patients, the average-sized patient (surface area 1.73 square meters) has an average normal value of 137 liters per 24 hours. Ideal body surface area in square meters in each patient was determined by use of the table for height and weight without clothing from the Life Extension Institute of New York City and the Du Bois Body Surface Chart. One-half pound for each week of pregnancy was added to the ideal nonpregnant weight.

$$\frac{1.73}{\text{Ideal body surface}} \times \text{actual clearance} = \text{corrected clearance}$$

$$\frac{\text{Corrected clearance}}{137} \times 100 = \text{per cent of normal}$$

Camara and his collaborators found the normal range in nonpregnant women to be 85 to 115 per cent, utilizing the actual body surface area.<sup>8</sup>

### Results in Group 1

In those patients with normal pregnancies, a wide variation was observed in the endogenous creatinine clearance (Fig. 1). In 32 normal pregnant women, 107 determinations were carried out during a period ranging from the seventh week of pregnancy to eight weeks post partum. Over 80 per cent of the antepartum determinations were above the normal nonpregnancy range. All antepartum tests were above 100 per cent. As the patients approached term there was a greater concentration of points in and near the normal nonpregnancy range. The elevation of glomerular filtration during pregnancy with a decrease near term suggested by these data is consistent with the observations of Bonsnes and Lange using the inulin clearance. From these endogenous creatinine clearances, a normal pregnancy range of from 100 to 180 per cent was established. After one week post partum, all clearances in the control series had dropped to the normal nonpregnancy range.

There was no consistency in the individual curves during pregnancy in the control series except for the decrease observed during the two weeks before delivery. This is illustrated in Fig. 2 by the creatinine clearances in 7 patients representative of Group 1. As was the case with the entire control group, there was wide individual fluctuation with increases as much as 60 per cent above the normal nonpregnancy range.

### Results in Group 2

A total of 128 antepartum and 32 postpartum creatinine clearances were determined in 9 patients with essential hypertension, 3 with diabetes mellitus, 2 with chronic renal disease, 9 with a history of previous pre-eclampsia or eclampsia, and one with a molar pregnancy.



Of the 9 patients with hypertension, 6 had clearances which were consistently normal and in none of these did signs of superimposed toxemia develop. Two of the hypertensive patients had a single clearance just below normal near term. The last patient in this group was a 35-year-old Negro nullipara who had a diagnosis of malignant hypertension established six months prior to conception. Four months before conception, she developed left cerebral artery

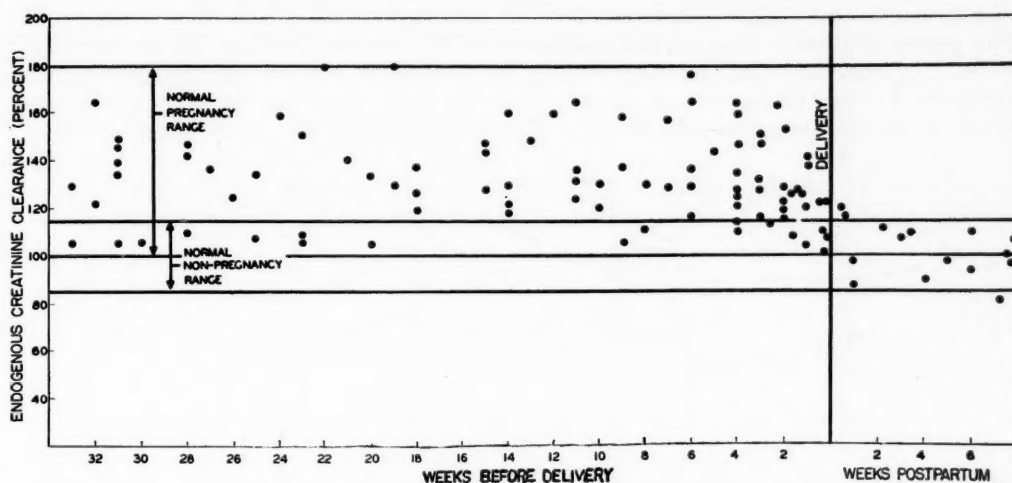


Fig. 1.—Endogenous creatinine clearances in 32 normal pregnant patients from the seventh week of pregnancy to eight weeks post partum, demonstrating increased glomerular filtration during pregnancy with return to normal, nonpregnancy levels post partum.

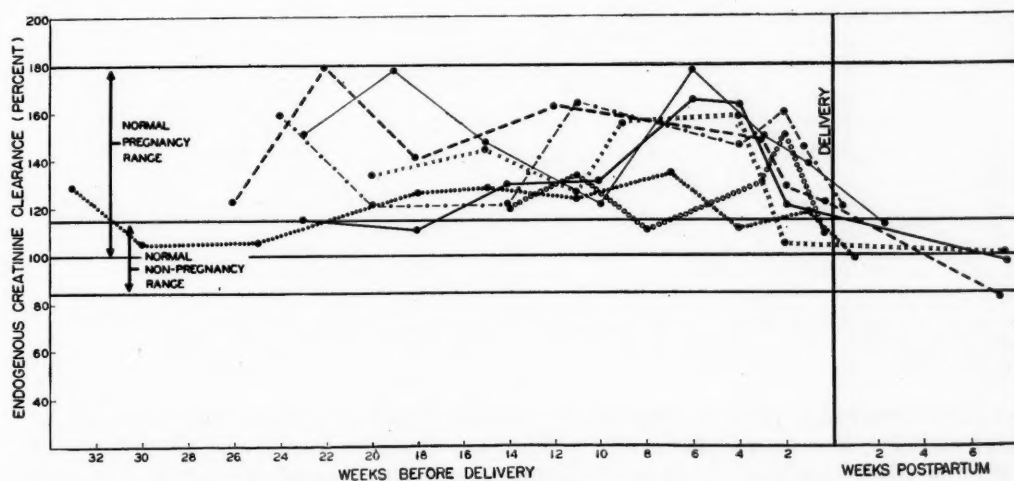


Fig. 2.—Endogenous creatinine clearances in 7 normal pregnant patients demonstrating a drop at or near term but otherwise no consistency in the antepartum curves.

thrombosis with residual hemiparesis. This patient's blood pressure, endogenous creatinine clearances, and urinary protein determinations are presented in Fig. 3. The first clearance was done at about the seventh month of pregnancy and was only 69 per cent with a urinary protein excretion of 0.6 Gm. in 24 hours and a blood pressure of 200/130 mm. Hg. One week later and two days before her delivery by cesarean section, the blood pressure rose to 240/150 mm. Hg, with the creatinine clearance further depressed to 33 per cent with an increase in

urinary protein to 2 Gm. per 24 hours. Post partum this patient's condition continued to deteriorate with persistence of marked hypertension averaging 250/150 mm. Hg, with a progressive decrease in glomerular filtration to less than 10 per cent a few days before her death. The proteinuria increased to 6 Gm. per 24 hours on the third postpartum day and subsequently fluctuated between 1 and 3 Gm. per 24 hours. The infant survived.

All 3 of the pregnant diabetic patients in this group started with normal clearance values which subsequently fell below normal. The first patient in this group showed a drop in her clearance to 90 per cent during the thirty-third week of pregnancy and by the time of her cesarean section during the thirty-sixth week the clearance had dropped to 70 per cent with no associated proteinuria or elevated blood pressure. The infant survived. The second patient

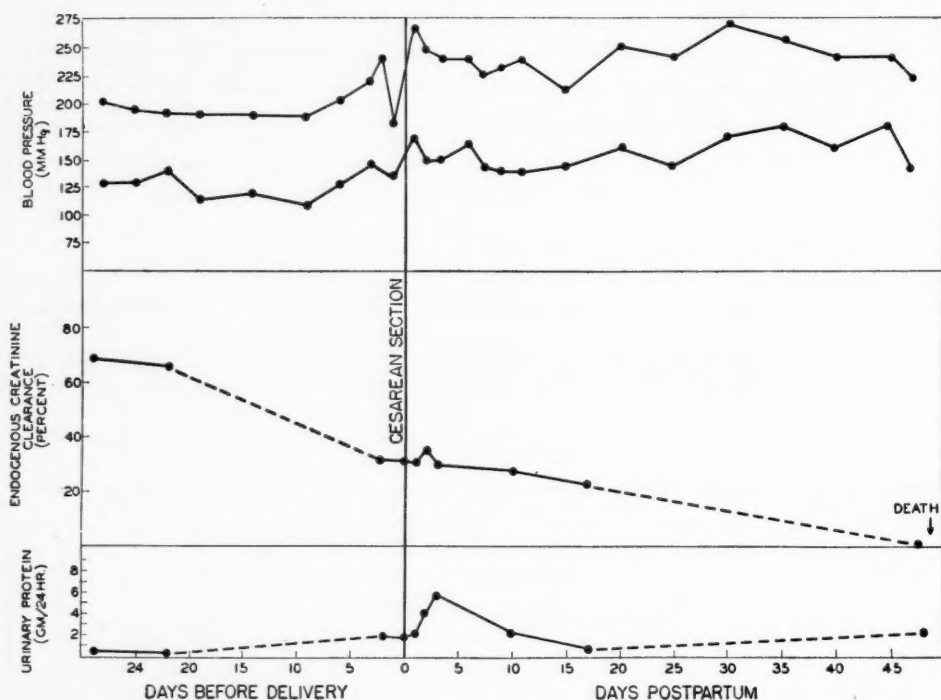


Fig. 3.—Blood pressure, creatinine clearances, and quantitative urinary protein excretions from a 35-year-old nullipara with malignant hypertension. The period of observation extended from the seventh month of pregnancy to the time of death on the forty-ninth postpartum day.

was a 26-year-old, para 0, gravida ii, who had had a spontaneous abortion at four months, five years previously (Fig. 4). She had been known to have diabetes mellitus for five years and chronic glomerulotubular nephritis for nine years. Throughout this patient's pregnancy, her blood pressure hovered around 140/90 mm. Hg and frequently fell within normal limits. The initial clearance during the tenth week of pregnancy was 145 per cent with a 24 hour urinary protein excretion of 5.5 Gm. and a blood pressure of 140/88 mm. Hg. By the twenty-fifth week, the creatinine clearance had dropped to 73 per cent with the same degree of proteinuria and slight elevation of the diastolic blood pressure. The creatinine clearances remained at a low level with an increase in the proteinuria to 8 Gm. in 24 hours. During the thirty-first week the clearance dropped to 46 per cent. At this point fetal death occurred. Although the blood pressure and urinary protein levels remained essentially unchanged, approximately two

weeks after fetal death and about two weeks before delivery, the creatinine clearance had risen to 89 per cent, which falls into the normal nonpregnancy range. During the third week post partum, the creatinine clearance remained normal

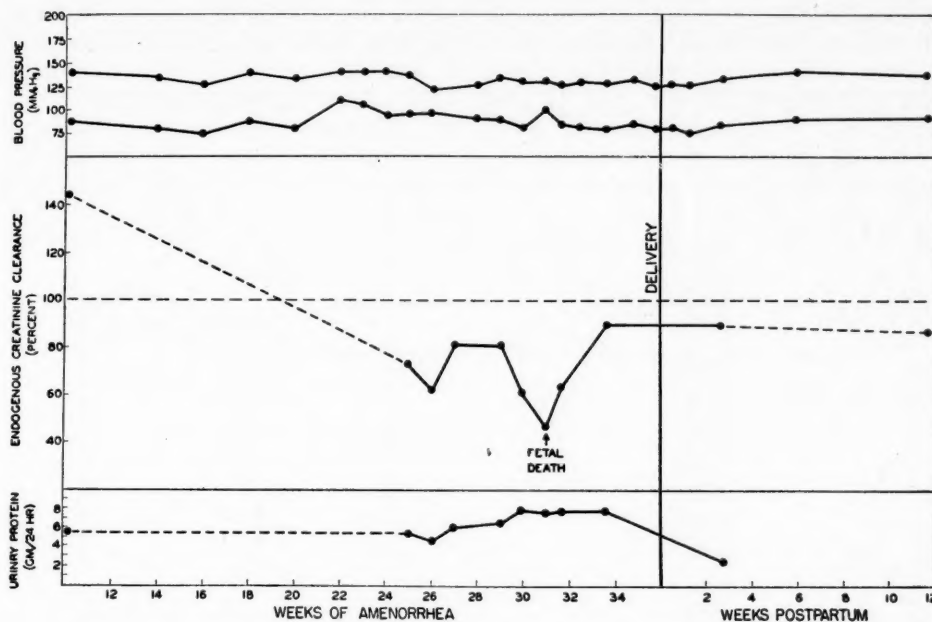


Fig. 4.—A 26-year-old pregnant diabetic patient with chronic nephritis. Note depression of creatinine clearance in advance of increased proteinuria, minimal fluctuation of blood pressure, and return of creatinine clearance to normal nonpregnancy range after fetal death.

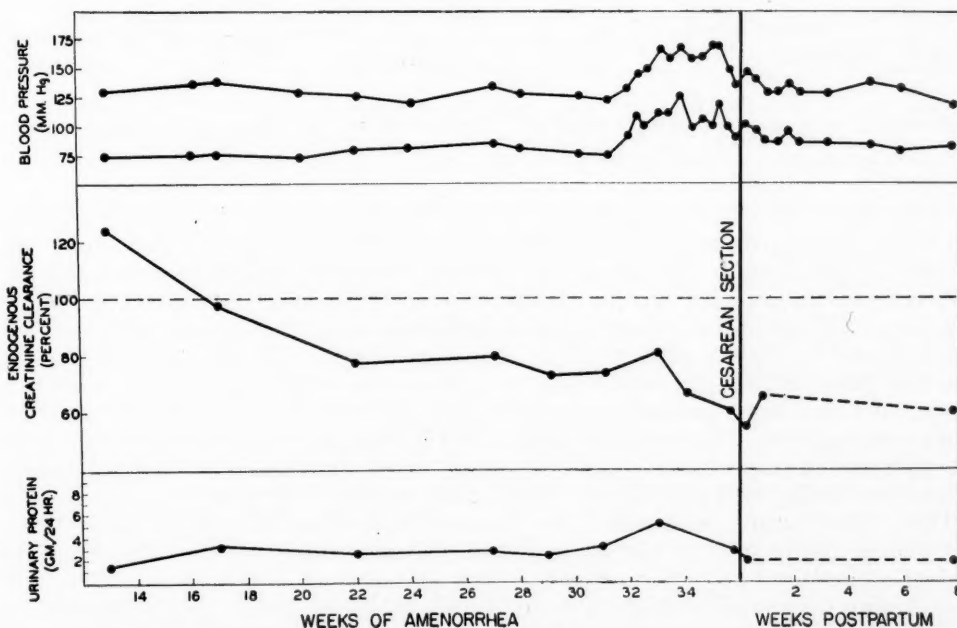


Fig. 5.—Blood pressure, creatinine clearances, and urinary protein excretions of a 25-year-old pregnant diabetic patient. Creatinine clearance was depressed 14 weeks before appearance of pre-eclampsia with persistence of depression post partum.

and the proteinuria had decreased to 2.5 Gm. in 24 hours. There was no appreciable change in the blood pressure post partum. The third patient in this group was a 25-year-old para 0, gravida ii, with severe diabetes, who had been known to have diabetes mellitus since the age of 14 years. For the past two years, she had had persistent albuminuria and microscopic hematuria and pyuria. At the time of her initial examination, during the thirteenth week of this pregnancy, the endogenous creatinine clearance was 124 per cent with a urinary protein excretion of 1.5 Gm. per 24 hours and a blood pressure of 130/74 mm. Hg (Fig. 5). By the seventeenth week, the clearance had dropped to 98 per cent with an increase in proteinuria to 3.2 Gm. per 24 hours. By the twenty-second week, the clearance had dropped further to 78 per cent with the protein

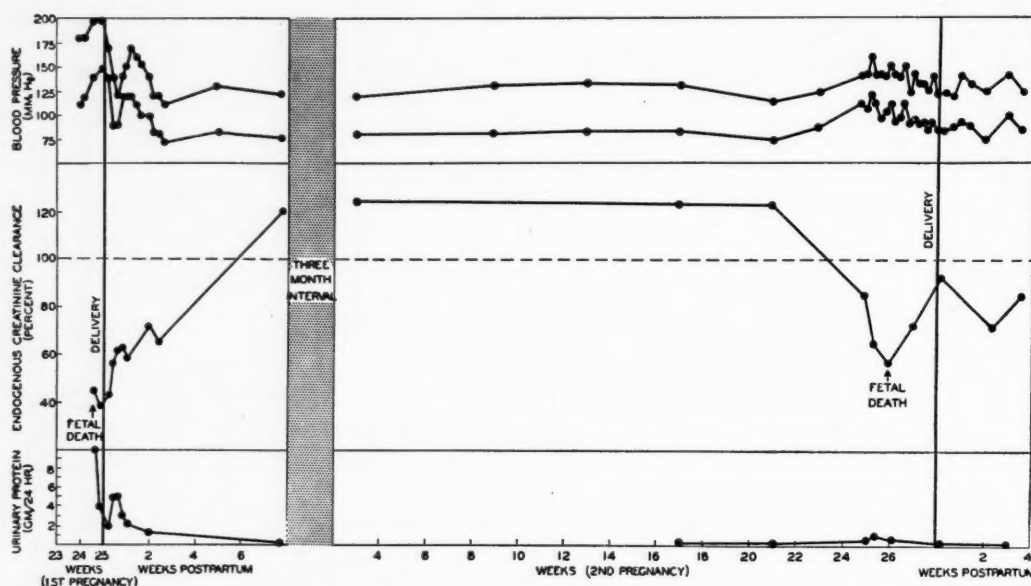


Fig. 6.—A 20-year-old patient who developed eclampsia during the twenty-fifth week of pregnancy with disappearance of proteinuria, hypertension, and depressed creatinine clearance post partum. During the next pregnancy, she developed pre-eclampsia with marked depression of creatinine clearance prior to fetal death.

excretion essentially unchanged and a normal blood pressure. During the thirty-first week and approximately 14 weeks after the first laboratory evidence of depression of glomerular filtration, the patient developed marked edema, hypertension, and an increase in the 24 hour protein to 5.3 Gm. By the time a cesarean section was done during the thirty-sixth week, the creatinine clearance had dropped to 60 per cent. After a further drop to 52 per cent during the first day post partum, the creatinine clearance rose to 65 per cent on the sixth postpartum day but remained depressed and was only 61 per cent almost eight weeks post partum. The urinary protein level remained at 2 Gm. per 24 hours. The postpartum clearances suggest residual renal damage as a consequence of the events during this pregnancy. The blood pressure returned to normal post partum. The infant survived.

Two patients with a history of renal disease presented no laboratory or clinical evidence of impaired renal function at the time of their initial examinations during pregnancy. Both had uncomplicated pregnancies with normal blood pressure, creatinine clearances, and urinary protein excretion.

Of the 9 patients in Group 2 with a history of previous pre-eclampsia or eclampsia, 8 had normal clinical and laboratory findings throughout. The re-



maining patient in this group was a 20-year-old, para 0, gravida ii, who had had a spontaneous abortion at about six weeks of pregnancy one year previously. She was first examined during the twenty-fourth week of pregnancy after eclampsia had become established. According to the referring physician, her blood pressure was normal during early pregnancy and she had developed no complications until four days previously when a blood pressure of 180/110 mm.

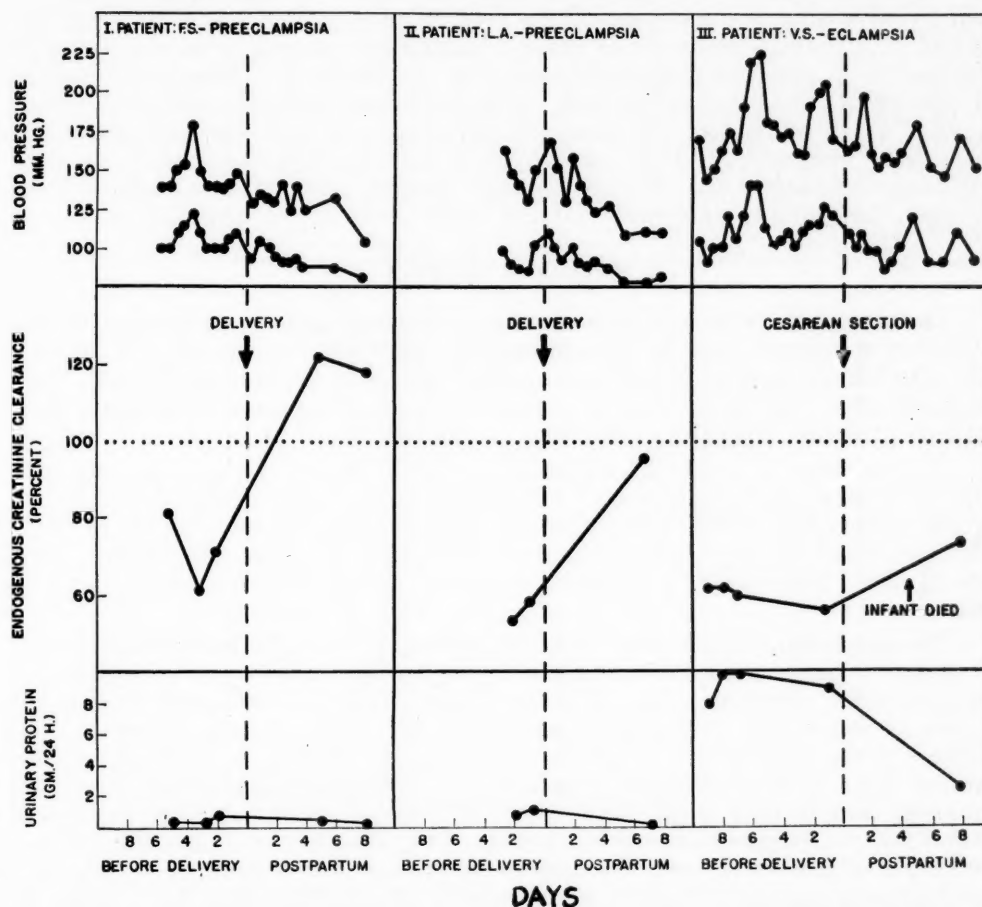


Fig. 7.—I, A 21-year-old para 0, gravida i, who developed pre-eclampsia during the thirty-sixth week of pregnancy with marked depression of creatinine clearance and slight proteinuria. Values returned to normal post partum. II, A 32-year-old para 0, gravida i, who developed pre-eclampsia during the thirty-sixth week of pregnancy with depressed creatinine clearance, slight proteinuria, and normal findings post partum. III, A 33-year-old nullipara who developed eclampsia during the thirtieth week with marked proteinuria and depression of creatinine clearance. Normal levels had not been re-established by the eighth postpartum day.

Hg and a 4 plus albuminuria were detected on a routine antepartum examination. Within twenty-four hours the patient developed convulsions and about forty-eight hours before her admission to the University of Michigan Hospital the fetal heart tones became imperceptible. At the time of her initial examination here the patient was comatose with a blood pressure of 180/120 mm. Hg, with a creatinine clearance of 45 per cent, and a urinary protein excretion of 10 Gm. per 24 hours (Fig. 6). Her blood pressure rose to a peak of 198/150 mm. Hg and the clearance dropped to 39 per cent during the day before delivery of a stillborn infant. During the first two weeks post partum, the blood

pressure dropped to 140/100 mm. Hg, with a rise in the creatinine clearance to 72 per cent. By eight weeks post partum, the patient had become normotensive with a normal creatinine clearance and quantitative urinary protein excretion. This patient was next examined about three and a half months later during the first month of her next pregnancy when she was still normotensive with a normal creatinine clearance. Again, she developed no difficulty until the twenty-fifth week of pregnancy when she developed signs of pre-eclampsia with hypertension, a depression of the creatinine clearance to 84 per cent and 0.5 Gm. of urinary protein per 24 hours. During the ensuing week, the clearance dropped to 55 per cent with the proteinuria increasing to 1 Gm. per 24 hours. At this point, fetal death occurred. One week later and one week before delivery of a stillborn infant, the clearance had risen to 72 per cent with disappearance of the proteinuria. Post partum the creatinine clearance rose to the non-pregnancy normal range and the patient became normotensive. Since then, however, the patient has demonstrated a labile, mild hypertension.

### Results in Group 3

In this group 36 antepartum and 34 postpartum creatinine clearances and quantitative urinary protein determinations were carried out on 10 patients with pre-eclampsia and 3 with eclampsia. All of these laboratory data were obtained after the appearance of clinical evidence of toxemia. None of these patients presented evidence of abnormality previously.

In retrospect, 6 primiparas had only mild evidence of pre-eclampsia with minimal edema, albuminuria, and hypertension of short duration. All 6 had normal endogenous creatinine clearances ante partum and post partum. Only 3 of the 7 had 24 hour urinary protein excretions in excess of 0.5 Gm. One with "mild" pre-eclampsia, however, excreted as much as 6.1 Gm. protein in 24 hours.

By comparison, the 4 remaining pre-eclamptic patients presented evidence of severe toxemia with more marked hypertension and severe depression of the creatinine clearance. In all 4 there was a poor correlation between the degree of proteinuria and other evidence of the severity of the toxemia. The findings in the first of these patients are presented in Fig. 7 (*I—F. S.*). This patient was a 21-year-old para 0, gravida i, who was normotensive and without apparent complication until the thirty-sixth week of gestation when hypertension and slight albuminuria were detected. One week later and five days before delivery her blood pressure was 140/100 mm. Hg with a creatinine clearance of 82 per cent and a 24 hour urinary protein of 0.3 Gm. Two days later, the clearance had dropped to 62 per cent with a rise to 72 per cent during the next 24 hours. After the appearance of hypertension, the blood pressure ante partum fluctuated between 140/100 and 180/124 mm. Hg. The quantity of urinary protein was essentially unchanged. Post partum the blood pressure returned to normal with a rise in the creatinine clearance to 122 and 118 per cent and disappearance of the slight albuminuria. This labor was medically induced and the infant survived. The second patient with severe pre-eclampsia was a 32-year-old para 0, gravida i (Fig. 7, *II—L. A.*) who appeared normal until the thirty-sixth week of pregnancy when she developed edema, albuminuria, and hypertension. During the 24 hours following detection of these signs of pre-eclampsia, the blood pressure averaged 165/100 mm. Hg and the creatinine clearance was decreased to 54 per cent with a proteinuria of 0.75 Gm. per 24 hours. One day later and one day before medical induction of labor and delivery, the creatinine clearance remained essentially unchanged with only a slight increase in the degree of proteinuria. Although this patient developed an intra-partum partial abruptio placentae, the infant survived. By the seventh post-

partum day the creatinine clearance had risen to a normal 98 per cent with a normal blood pressure and the disappearance of the edema and albuminuria. Another pre-eclamptic patient presented clinical and laboratory findings comparable to those of the two patients just discussed. The last in this group had pre-eclampsia associated with a molar pregnancy. This case will be discussed later (Fig. 8).

One of the 3 cases of eclampsia has been presented in detail (Fig. 6). The data from a second patient with eclampsia are presented in Fig. 7 (III—V. S.). This patient was a 33-year-old para 0, gravida i, who developed recent excessive weight gain, edema, albuminuria, and hypertension. These signs of toxemia progressively increased in severity and three weeks later she developed convulsions. One day later she was first examined at the University of Michigan Hospital when the blood pressure was 170/110 mm. Hg, with a creatinine clearance of only 62 per cent and a 24 hour urinary protein excretion of 8 Gm. The

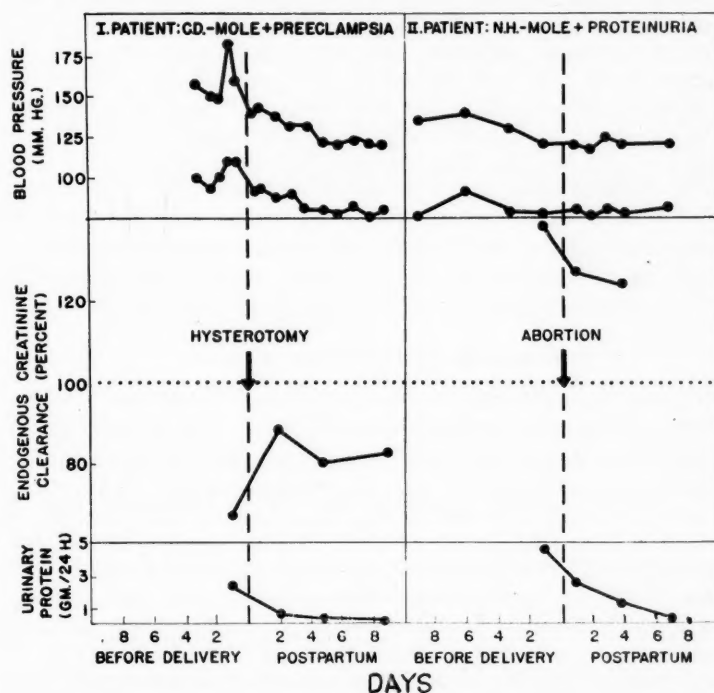


Fig. 8.—I, A 26-year-old para ii, gravida iii, with a molar pregnancy, pre-eclampsia, marked depression of creatinine clearance, and proteinuria. II, A 25-year-old para ii, gravida iii, with a molar pregnancy, proteinuria, normal creatinine clearances, and normal blood pressure.

patient remained comatose during the ensuing seven days and the convulsions were controlled with sedation. The creatinine clearance was further depressed to 56 per cent with an increase in proteinuria to 10 Gm. per 24 hours. After repeated attempts to induce labor had failed, cesarean section was carried out with the delivery of a 3 pound infant who died on the fourth day. When this patient was last examined on the eighth postpartum day, the creatinine clearance had risen to 74 per cent with a decrease in the proteinuria to 2.5 Gm. per 24 hours and blood pressure of 150/92 mm. Hg. A longer period of observation, which was not possible in this patient, would be essential to assess the degree of residual hypertension and renal damage. The last eclamptic patient was a 16-year-old primagravida who appeared normal until albuminuria was detected

during labor. During the first 24 hours post partum, hypertension and a convulsion developed. The following day, the creatinine clearance was within the lower limits of normal with 1.1 Gm. urinary protein per 24 hours. During the next two days the patient became normotensive with a further increase in the creatinine clearance and disappearance of the albuminuria a few days later.

### Molar Pregnancies

There were two molar pregnancies—one in Group 2 and another in Group 3 (Fig. 8). The first patient was a 26-year-old, para ii, gravida iii. Beginning during the seventh week of pregnancy, daily vaginal bleeding occurred for two months. At about 3½ months of gestation, edema, albuminuria, and hypertension developed with subsequent fluctuation of the blood pressure between 150/90 and 185/110 mm. Hg. Two weeks later, the initial creatinine clearance was only 67 per cent with a 24 hour urinary protein excretion of 2.3 Gm. One day later, an abdominal hysterotomy was carried out with evacuation of the mole from a uterus compatible in size with that of a six-month pregnancy. During the first two days post partum, the blood pressure fell to normal with an increase in the creatinine clearance to 88 per cent and disappearance of the proteinuria. The second patient (Fig. 8, II—N. H.) was a 25-year-old para ii, gravida iii, who developed vaginal bleeding during the third month of pregnancy. This recurred at frequent intervals and one month later albuminuria appeared. On isolated occasions, the blood pressure rose as high as 140/90 mm. Hg. At the end of the fifth month of pregnancy, the creatinine clearance was 138 per cent with a 24 hour urinary protein excretion of 4.7 Gm. After a Pitocin induction, a molar abortion was completed by uterine curettage. Post partum the patient remained normotensive with normal creatinine clearances and disappearance of the proteinuria.

### Blood Serum Creatinine

Using the Bonsnes and Taussky method, Camara found the range of blood serum creatinine in normal nonpregnant women to be 0.77 to 0.98 mg. per cent with an average of 0.86 mg. per cent. In our control series of normal pregnant women, the serum creatinine was less, with a range of 0.48 to 0.86 mg. per cent with an arithmetical mean of 0.64 mg. per cent. This reduction contributes to the higher clearance values during pregnancy and is a reflection of the hypervolemia of pregnancy and associated increased glomerular filtration. After one week post partum all of the serum creatinine values in the control series were within Camara's normal range. In contrast to the clearances, a single blood serum creatinine determination was of practically no value in the early detection of impaired renal function. With serial determinations in the same patient there was generally an increase in the blood serum creatinine by the time the creatinine clearance was depressed in the presence of progressive renal disease. During an early stage of renal impairment, however, the blood serum creatinine often remained within the accepted normal range and was elevated only in comparison with previous determinations in the same patient.

### Cord Blood and Amniotic Fluid Creatinine

In 25 normal patients, specimens of blood were obtained from the mother and the umbilical cord immediately after delivery. The creatinine content of maternal and cord blood was practically the same with an average difference of only 0.02 mg. per cent. These data suggest that there is no placental barrier in so far as creatinine is concerned. The maternal blood serum values in this group were higher on the average than those observed before term and all were within the normal nonpregnancy range. The rise in the blood creatinine is further reflected by the lower clearances at this stage.



In 22 normal patients, the creatinine content of amniotic fluid obtained when the membranes were ruptured artificially immediately before delivery ranged from 1.27 to 3.29 mg. per cent with an average of 2.38 mg. per cent. In 10 of these patients, specimens were obtained simultaneously from the maternal and cord blood and amniotic fluid. The creatinine content of the amniotic fluid was 2 to 3.5 times greater than in the maternal or cord blood with an average of 3 times as much. The creatinine content of amniotic fluid is probably related to fetal excretion.

#### Total Serum Proteins

Serum protein determinations in the three groups of patients were consistent with previous observations.<sup>14</sup> In the normal pregnant patients, the average serum protein concentration was 6.2 Gm. per cent. This average would probably have been somewhat higher had more determinations been made prior to the last trimester of pregnancy when these values were generally lower.

There was an even greater reduction in serum proteins in the toxemic patients, with an average of only 5.36 Gm. per cent. There was no clear correlation between the degree of reduction of serum proteins and the clinical status of the toxemia.

#### Summary

A method of measuring glomerular filtration during pregnancy by use of the 24 hour endogenous creatinine clearance test is described. This method is compared with other measures of renal function during pregnancy.

Antepartum and postpartum quantitative creatinine and protein determinations in both blood and urine were carried out in three groups of patients: (1) control series of normal pregnant women, (2) patients with diseases or medical histories predisposing them to the development of toxemia, and (3) those patients not included in Group 2 who developed pre-eclampsia-eclampsia. In an additional series of normal women, the creatinine content of maternal and cord blood and amniotic fluid were determined from specimens obtained at the time of delivery.

An increase in the endogenous creatinine clearance from early pregnancy with a decrease at or near term was observed in normal patients. A normal range during pregnancy was established.

Decreases in the creatinine clearances paralleled the clinical evidence of severity of the toxemias of pregnancy. Little or no decrease was observed in those patients with slight evidence of pre-eclampsia, suggesting that depression of the glomerular filtration is not an early change. However, further experience with more frequent clearances will be essential to establish whether or not the creatinine clearance may serve as an early index of the development of pre-eclampsia-eclampsia. The creatinine clearance indicated depressed renal function earlier than did the blood serum creatinine alone.

All three of the pregnant diabetic patients studied started out with normal clearances which subsequently were depressed well in advance of clinical evidence of superimposed pre-eclampsia. If these observations are repeated in a larger group, such testing would be of real prognostic value in the management of the pregnant diabetic.

In most of the patients with toxemia there was a poor correlation between the quantitative blood serum and urinary protein and the creatinine clearance and clinical severity of the toxemia.

On the basis of our experience to date we believe that the endogenous creatinine clearance test has proved to be a practical and clinically useful means of measuring renal function during pregnancy as well as evaluating residual renal effects of the toxemias of pregnancy.

I wish to acknowledge my indebtedness to Drs. Henry K. Schoch and Augusto A. Camara for their invaluable advice during the conduct of this study, and to Mrs. Beth Flemings, who performed all of the laboratory procedures herein reported.

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## A STUDY OF HUMORAL VASOEXCITOR AND DEPRESSOR MATERIALS PRESENT IN TOXEMIA

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THE toxemias of pregnancy continue to be an enigma. This paper discusses only a limited aspect of the problem: the similarities of the hypertensive phase of toxemia and essential hypertension, with particular reference to the vasoexcitor and depressor materials described by Zweifach and Shorr.<sup>1</sup>

In the capillary bed, the arterioles terminate in the metarterioles, in whose walls the muscle cells are scattered, rather than in a continuous layer. Depending on the degree of fluctuation of metabolic needs of the tissues, some metarterioles end in a group of capillaries, while others continue on, and eventually double back upon themselves, being joined by true capillaries to form venules. These vessels are known as preferential channels, and supply the basic needs of the tissues, while the capillary groups constitute a reserve network used in time of stress.<sup>2, 3</sup> About the base of each capillary are one or two muscle cells, so placed as to have a sphincteric action, which are called precapillary sphincters. The circulation in the capillary bed continually fluctuates from preferential channels to the entire system even under normal conditions, due to irregular constrictions of these precapillary sphincters, and this phenomenon is known as vasomotion. When vasomotion is increased, the number of cycles rises and the constrictor phase becomes more prominent; the opposite is true when vasomotion is depressed. This is significant in that when the active circulation is restricted to the preferential channels, the remainder of the capillary bed is available for inward filtration and hemodilution.<sup>4</sup> Shorr and Zweifach,<sup>1</sup> studying the effect of graded hemorrhage on the terminal vascular bed of exteriorized omentum of anesthetized dogs,<sup>5, 6</sup> observed that in the initial or compensatory phase of shock, there is marked increase in vasomotion<sup>7</sup> and an increase in sensitivity of muscular vessels to topically applied epinephrine. When shock was prolonged to the decompensatory stage, the opposite was true. When plasma from these dogs was injected intravenously into anesthetized normal rats, the mesoappendix vessels of the latter exhibited the identical changes in vasomotion and epinephrine sensitivity, although the blood pressure of the rats remained unchanged.<sup>6, 8</sup> This constitutes the basis for the rat mesoappendix test.<sup>9</sup> That the material responsible for these changes is tissue in origin and humoral in nature has been demonstrated by Zweifach, Shorr, and others. Tissue washes taken from these animals in shock have made it apparent that, in the initial or compensatory phase, vasoexcitor material is produced by the kidney, but, as shock is prolonged, vasodepressor material appears from liver and skeletal

muscle in amounts to neutralize and eventually override the vasoexcitor material.<sup>10</sup> That tissue anoxia is present in shock has been shown by Engel and others.<sup>11, 12</sup> By anaerobic and aerobic incubation of tissues taken from normal animals it has been demonstrated that the normal kidney produces vasoexcitor material under anaerobic conditions and will inactivate it under aerobic conditions, but if anaerobiosis is prolonged, it loses its ability to inactivate and continues to produce vasoexcitor material even under aerobic conditions. Liver and skeletal muscle behave in the same fashion in respect to vasodepressor material. In experiments using the Goldblatt clamp, Zweifach and others<sup>13</sup> have found that vasoexcitor material is present in the blood of hypertensive animals, although, as the situation is prolonged, it is masked by the presence of vasodepressor material. Table I summarizes these observations. Shorr<sup>14, 15</sup> has demonstrated the presence of vasoexcitor material in the peripheral blood of human hypertensive patients. Lee and Holze<sup>16</sup> have shown that the sensitivity to topical epinephrine of the vessels of the bulbar conjunctiva is increased in human hypertensive patients. Catheterization studies of human renal venous blood by Edelman, Zweifach, and associates<sup>17</sup> have demonstrated that anoxia, whether from congestive heart failure or from the breathing by normal individuals of mixtures of 90 per cent nitrogen and 10 per cent oxygen, will cause production of vasoexcitor material.

TABLE I

	AEROBIC CONDITIONS	ANAEROBIC CONDITIONS
Normal kidney	Inactivates vem	Produces vem
Normal kidney incubated anaerobically	Produces vem and loses	Produces vem
Hypertensive kidney	ability to inactivate	
Hyporeactive shock kidney		
Normal liver	Inactivates vem and vdm	Produces vdm
Normal liver incubated anaerobically	Produces vdm and loses	Produces vdm
Hypertensive liver	ability to inactivate both	
Hyporeactive shock liver		

The chemical nature of vasoexcitor material has not been identified. It is a polypeptide, but as yet cannot be purified. It differs from renin and angiotonin, in that it has no effect on the blood pressure. Although angiotonin will potentiate the sensitivity of the rat mesoappendix, it is believed that contamination with vasoexcitor material in all available samples is responsible.<sup>18</sup> Vasodepressor material has been identified as ferritin by spectroscopic methods.<sup>19</sup> Ferritin was first isolated by Laufberger in 1937. It serves in the liver as a mechanism for the storage of iron, and—as apoferritin—ferritin regulates the absorption of iron from the gastrointestinal tract. It may also serve in the absorption of iron by the placenta, and in the reabsorption of iron by the renal tubule.<sup>20, 21</sup>

The possibility is suggested that, due to repeated episodes of relative renal anoxia, perhaps neurogenic in origin, the kidney finally begins to produce vasoexcitor material under aerobic conditions. Because of relative anoxia



resultant from the increased metarteriolar and precapillary sphincter sensitivity to circulating epinephrine, caused by the vasoexcitor material, the arterioles tend to constrict and pressure rises. With the hepatic anoxia increasing, vaso-depressor material appears, and to a certain extent neutralizes the vasoexcitor material, but permanent changes have taken place by then, and hypertension continues. Although essential hypertension and toxemia of pregnancy have many dissimilarities, they have vasospasm in common. So it is not surprising that when Shorr and Zweifach<sup>22</sup> tested the peripheral blood of eight patients with pre-eclampsia, they found large amounts of both vasoexcitor and depressor materials present. The plasma of normal pregnant patients had none of either factor.

Lee and Holze<sup>23</sup> studied the bulbar conjunctiva of three patients who had toxemia and had apparently recovered, in that they had since been normotensive for four months to three years. All showed constricted conjunctival metarterioles and two showed increased epinephrine sensitivity.

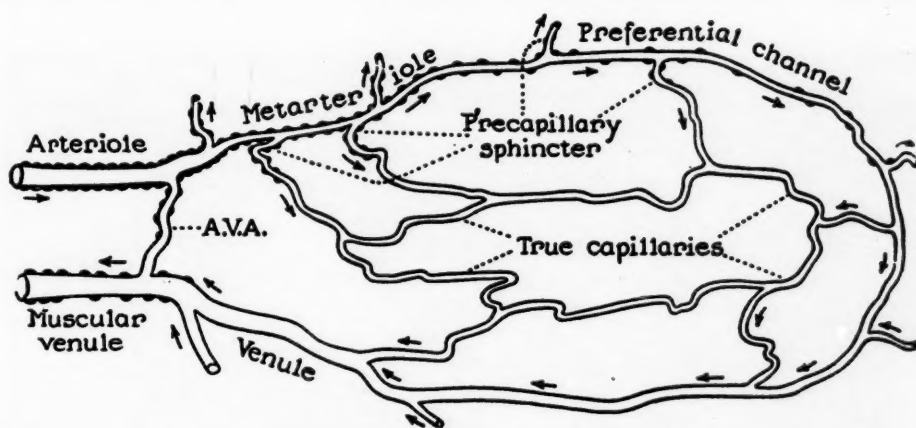


Fig. 1.—A diagrammatic representation of the architecture of the capillary bed. (From Zweifach, B. W.: Transactions of the Third Conference on Factors Regulating Blood Pressure, New York, 1949, Josiah Macy, Jr., Foundation.)

Much evidence has accumulated to implicate the placenta as a possible source of materials involved in the pathogenesis of toxemia. Dieckmann<sup>24</sup> believes that placental tissue, meaning both maternal and fetal, must be given much more consideration with reference to the etiology of pre-eclampsia and eclampsia. Studies of placental circulation by Fournier<sup>25</sup> and others show evidence that in mild and prolonged albuminuria there is gradual obliteration of placental capillary circulation to the point of arterial stasis. Bartholomew has made an extensive study of placental pathology and is convinced that impairment of circulation, with subsequent tissue necrosis, is responsible for eclampsia. We know that the placenta, in addition to being an organ for the transfer of metabolites, also produces estrogens, progesterone, chorionic gonadotropin, enzymes, and is a potential source for large amounts of thromboplastin. Accordingly, it was thought that it would be worth while to determine whether

or not it was a source of vasoexcitor or depressor material although others have investigated this source without positive results for substances causing changes in blood pressure.<sup>26</sup>

### Materials and Methods

Immediately following delivery, a wedge-shaped section of the placenta, including maternal and fetal surfaces and a portion of membranes, was cut. This was washed with iced physiological saline solution, and then cut into as fine slices as possible. These particles were washed five to seven times more with iced saline until the blood had been removed. The tissue was pressed as dry as possible between layers of gauze, and then mixed with approximately five times its volume of glucose Ringer's solution. This was incubated under anaerobic conditions with constant agitation at 37.5° C. for one hour. The material was centrifuged and tested for vasoactivity by the rat mesoappendix test. This procedure was carried out on eight placentas. Seven were from normotensive mothers at term, following uncomplicated labors and deliveries of normal infants under regional block anesthesia. All tested neutral. On three occasions, an aliquot of the fluid was incubated aerobically with slices of normal dog kidney to unmask possible vasodepressor material. None was found.

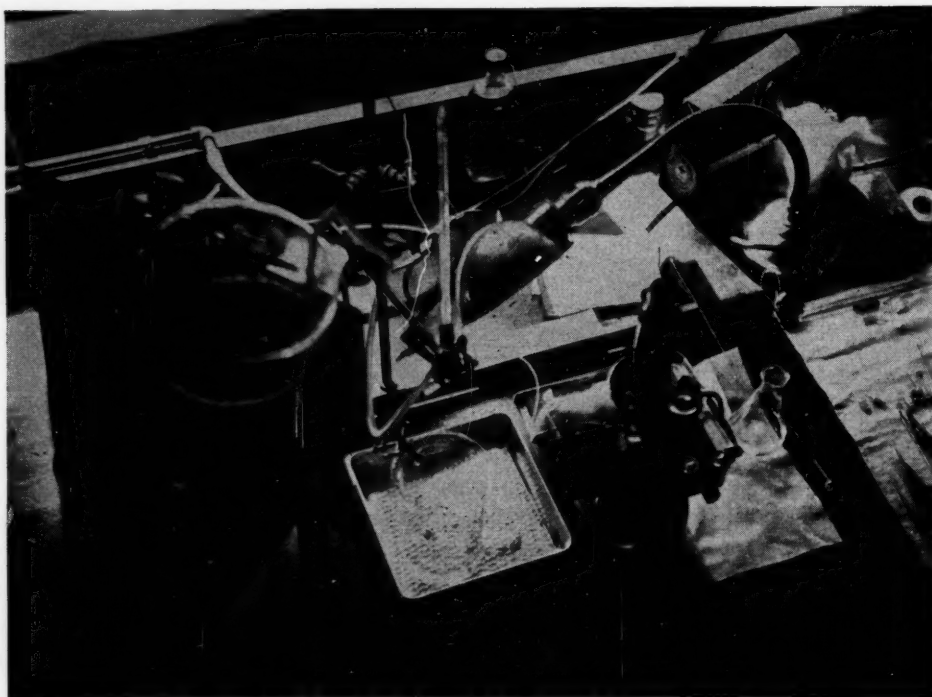


Fig. 2.—The rat mesoappendix test. The mesoappendix of the anesthetized animal is draped over a Lucite block and constantly moistened with Ringer's solution the temperature of which is carefully controlled. The different dilutions of epinephrine solution are sprayed directly on the mesoappendix vessels from the tuberculin syringe. The substances to be tested are injected into the tail vein.

Five cubic centimeters of venous blood, with 0.1 ml. of heparin added, was obtained from 19 patients. Five were at term but not in labor. Four had been in labor from two to twenty-four hours and the cervix was from 2 to 9 cm. dilated. Seven were taken at delivery, all under regional block. Three were

from four to twelve hours post partum. All were normotensive. The blood specimens were immediately chilled and centrifuged within fifteen minutes. The plasma specimens were refrigerated until tested. All were neutral. An aliquot of 3 of those taken at delivery was incubated aerobically with normal dog kidney. No vasodepressor material was unmasked. Five samples of cord blood of normal full-term infants were taken and tested. All were neutral. This is summarized in Table II.

TABLE II

TESTED FOR VASOACTIVITY	ANAEROBICALLY INCUBATED AND TESTED
Venous blood	7 normal placentas
5 at term	1 pre-eclampsia placenta
4 in labor	
7 at delivery	Aliquot incubated aerobically with
3 post partum	normal kidney slices
5 cord blood specimens	3 normal placentas
	1 pre-eclampsia placenta
Aliquot incubated aerobically	
with normal kidney slices	
3 at delivery	

We had the opportunity of observing one patient with pre-eclampsia.

She was a 36-year-old para i, gravida iv, whose first pregnancy went to term, and was followed by two deliveries of previable infants. She had no history of previous renal disease or toxemia. At thirty-four weeks of gestation, her blood pressure abruptly rose to 160/110 and a trace of albumin appeared in the urine. Two days after this, with her pressure the same and the twenty-four-hour albumin output 0.13 Gm., the peripheral blood tested moderately positive for vasoexcitor material. Three days after the first test, the blood was strongly positive. Ten days later, with conditions apparently unchanged, the blood tested neutral, but incubation of another sample the next day with normal dog kidney unmasked a moderate amount of vasodepressor material. Fifteen days after the first test, she delivered a somewhat premature infant who survived, apparently undamaged. A sample of the placenta was incubated anerobically and tested for vasoactivity, and an aliquot of the solution was incubated with normal dog kidney and retested. Neither vasoexcitor nor depressor material was found.

### Comment

There are several other points about all this that may be worth mention. One is that it is literally impossible to produce irreversible shock in unanesthetized dogs. They invariably respond favorably to transfusions. Vasoexcitor material is present in their peripheral blood, but vasodepressor material never appears, even at the point of death.<sup>27</sup>

The intact and functioning adrenal is necessary for vasoexcitor production, kidneys from adrenalectomized rats, cats, dogs, and rabbits produce none.<sup>27</sup>

Shroeder<sup>28</sup> has obtained positive rat mesoappendix tests with many other materials than vasoexcitor material, and suggests that the test may be much more sensitive than blood pressure changes, and that if vasoexcitor material could be concentrated, it might prove to be a vasopressor.

Grollman,<sup>29</sup> by use of the artificial kidney, has been able to keep dogs alive and in fairly good health for many weeks after both kidneys had been removed. All of these dogs became hypertensive in time. Although the number was small, this work casts some doubt on the whole idea of the renal origin of hypertension.

Pickering<sup>30</sup> succeeded in giving a rabbit renin by continuous intravenous drip for three weeks. During the infusion the pressure rose, but as soon as it was stopped it fell to normal. Until vasoexcitor material can be purified and concentrated, and perhaps some such similar experiment carried out, the role of this material in the pathogenesis of hypertension and toxemia will remain obscure.

### Conclusions

We agree with Zweifach and Shorr's observations that vasoexcitor and vasodepressor materials are present in the peripheral blood of patients with pre-eclampsia and that the blood of normal controls is neutral. The stress of labor and delivery under regional block anesthesia was not enough to produce vasoexcitor or depressor materials in the peripheral blood of mothers or infants in our series. Although the placenta may well contain ferritin, it apparently is not in a vasoactive form, nor were we able to get the placenta to produce vasoexcitor material.

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## THE CRUSH SYNDROME IN OBSTETRICS\*

### Report of Fatal Case

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IN 1941, Bywaters and Beall<sup>1</sup> reported four cases of renal failure following crushing injury to the extremities and defined this entity as the crush syndrome. Cases of renal failure developing in the course of diseases not affecting the kidneys directly had been known for many years under the name of hepatorenal syndrome, but had aroused little interest until this report.

As further case reports were forthcoming, it became apparent that the term crush syndrome was a misnomer, since a wide variety of etiological agents were found to produce the identical clinical and pathological picture, and the term lower nephron nephrosis was suggested for this condition.<sup>2</sup> The terms reflex anuria and toxic anuria are also used, but do not fit all cases, since a neural or toxic mechanism cannot always be demonstrated.

Traumatic conditions producing the crush syndrome in addition to the original crushing injuries are wounds, surgical procedures, heat stroke, and burns. Incompatible transfusions, with or without intravascular hemolysis, are a very common cause of the crush syndrome. Similar lesions have been noted in malaria, due to the hemolytic changes of blackwater fever. Acute hemolytic anemia of any type may give rise to anuria. Various infectious processes may terminate in anuria, but in some cases direct infection of the kidneys may be responsible. The anuria observed in terminal nephritis is produced by a different mechanism from that of lower nephron nephrosis, but many valuable methods of treatment have been developed from this type of case, and the same is true of mercury and alcohol poisoning.

The occurrence of the crush syndrome in obstetrical conditions was noted by Young and McMichael<sup>3</sup> shortly after the original reports. The original cases were prolonged and difficult labor, but toxemia, abortion, and especially premature separation of the placenta have also been reported as causes.

Anuria from sulfonamide intoxication is usually mechanical in nature as is that following renal calculus, being due to obstruction to the outflow of urine, rather than lack of secretion, but may pass into true anuria if untreated. A similar lesion has been described following x-ray therapy.<sup>4</sup> In this case precipitation of uric acid crystals in the pelvis of the kidney caused complete obstruction.

Considerable experimental work has been done on these lesions. It is impossible to rule out the mechanical factor in any case of reflex anuria. The

\*The views expressed in this paper are those of the author and do not necessarily represent those of the Indian Service.

pigment theory (Young) suggests that even in crush and hemolytic injuries there may be an obstruction due to the precipitation of hematin crystals (derived from hemoglobin or myohemoglobin) within the collecting tubules. Alkalosis is necessary for this process and vomiting is often found preceding anuria.<sup>5</sup> In many cases hematin casts are noted in the collecting tubules and the distal portion of the convoluted tubules. Patchy areas of degeneration and necrosis are also noted in these areas.<sup>2</sup>

The damage may also cause unselective resorption of all fluid and substances secreted by the glomerulus by permitting them to leak into the adjacent tissues. Against this theory is the failure of resorption and unselective excretion found during the recovery stage.

The neural theory proposes that the filtration pressure within the glomerulus is reduced to ineffective levels by reflex vasoconstriction of the arterioles. Ischemia and shock are certainly frequently found in these cases, but anuria will persist despite restoration of adequate blood flow in observable parts of the body and interruption of all nerves to the renal arterioles. The production of anuria experimentally by constriction of the kidney by ligation of the renal arteries cannot be considered to represent the course of events in crushing injuries.

Finally, unknown substances may be released by injured tissues which exert a direct toxic effect on the glomerular or tubular cells to suppress the formation of urine. Such substances have not been isolated, nor has any convincing evidence of their existence been elicited. The crush syndrome may be produced in one individual, while another with a similar or even more severe lesion will escape, so that some individual variation in response is partially responsible for these cases.

The case to be presented is typical of the obstetrical group, in both development and ultimate outcome, premature separation of the placenta and toxemia being common causes of the crush syndrome. Premature separation of the placenta affords the opportunity for myohemoglobin and other products of muscle breakdown to be released into the circulation, while toxemia reduces the capacity of the kidneys to deal with these products. Whatever the cause, the result is a bizarre and highly dangerous sequence of events.

### Report of Case

A 30-year-old gravida iv, para iii, was admitted to the hospital on Feb. 2, 1954, at 6:00 A.M., with the history of having fallen on her abdomen approximately twelve hours before admission. Shortly after falling, she developed irregular abdominal cramping and moderate vaginal bleeding, both of which had persisted to the time of admission.

As far as could be determined, the previous pregnancies had been normal. The patient had felt well during the present pregnancy and had not sought prenatal care. The last menstrual period was in August, exact date unknown. No other relevant material was developed from the history.

Physical examination revealed an acutely ill woman, very pale, in some pain and quite apprehensive. The temperature was 98° F., pulse 74, and respiration 20. The blood pressure was 174/110. The pregnancy was of approximately 6 months' duration, the fetal heart tones

were not heard, and slight vaginal bleeding was noted. The remainder of the examination was negative. There were no evidences of toxemia. Laboratory reports were as follows: White blood count 17,900, red blood count 2.23 million, hemoglobin 4.5 Gm. per 100 c.c. of blood, nonprotein nitrogen 70 mg. per cent. On catheterization, 30 c.c. of amber urine was obtained which gave a 4 plus reaction for albumin, and contained many red cells, pus cells, and hyaline casts.

The diagnosis on admission was premature separation of the placenta, probable fetal death, and possible pre-eclampsia. Immediate treatment consisted of sedation and complete bed rest, both to control the pre-eclampsia and to preserve the fetus if still viable.

*Hospital Course.—*

After admission the patient continued to have irregular uterine contractions of considerable force. She complained of nausea, but did not vomit. The blood pressure rose to 220/108. Vaginal examination was performed and revealed a cephalic presentation with an extremely soft fetal head, confirming the impression of fetal death. Accordingly, attempts to conserve the pregnancy were abandoned in favor of rapid evacuation of the uterus. During this procedure the patient was catheterized to obtain the admission specimen previously mentioned. The cervix admitted a forceps which was used to rupture the membranes and delivery of a nonviable male fetus of approximately 6 months' gestation occurred one hour later at 12:25 P.M. The blood pressure remained elevated following delivery. No urine was obtained on catheterization at 3:30 P.M. and the probability of reflex anuria was considered. Five per cent dextrose in water was given intravenously with no result. At 10:00 P.M., procaine in saline was given intravenously. No response was manifested and spinal anesthesia was induced the following morning. During the day the patient received 500 c.c. of whole blood, 1,000 c.c. of 10 per cent glucose in water, and 1,000 c.c. of 5 per cent glucose with 20 mg. of Pontocaine. On the evening of the second day she developed edema of the extremities and became listless, but not comatose. Parenteral fluids were discontinued and peritoneal irrigation was instituted.

TABLE I. PERITONEAL IRRIGATION

	INTAKE		OUTFLOW
2-4-54	1,000 c.c.	5% dextrose	850 c.c.
	1,000	Saline	2,500
	1,000	5% dextrose	400
	600	5% dextrose	250
Total	3,600 c.c.		4,000 c.c.
2-5-54	1,000	Tyrode's	180
	1,000	Tyrode's	450
Total	2,000 c.c.		630 c.c.
2-6-54	1,000	Tyrode's	1,400
	1,000	Saline	-
Total	2,000 c.c.		1,400 c.c.
2-7-54	1,000	Tyrode's	700
	1,000	Dextrose	-
Total	2,000 c.c.		700 c.c.
Grand total	9,600 c.c.		6,730 c.c.

Rather complicated apparatus has been employed by other writers who have used peritoneal irrigation.<sup>6</sup> We did not have these facilities available and used a very simple system which was quite successful in the early period. Ordinary intravenous solutions of 5 per cent dextrose in water were introduced into the peritoneal cavity just above the umbilicus through a 19 gauge needle. About 6 inches to the right, a 17 gauge needle was inserted and attached with sterile tubing to a collection bottle. Various solutions were employed later, including modified Tyrode's saline and distilled water. The glucose solution seemed superior to the

others in removing excess fluid and was much simpler than the Tyrode's in preparation. We became dissatisfied with the rate of outflow and introduced a catheter, and still later a metal sump drain. Table I shows the input and outflow during the period of irrigation. After the catheter was introduced considerable leakage around the tube developed and the actual outflow was considerably more than the measured amount during the last two days.

The nonprotein nitrogen rose to 78 on February 4, 113 on February 5, and 130 mg. per cent on February 6. The nonprotein nitrogen of the outflow fluid was higher than the blood nonprotein nitrogen by a few points, probably representing a normal variation in accuracy.

Although the patient had no urinary output, her condition appeared to stabilize until February 6, when cough and basal râles developed. Pulmonary edema progressed, blood-tinged sputum appeared, and the patient died at 11:15 P.M. on Feb. 7, 1954, six days following the development of anuria. She remained mentally alert and took food and fluids by mouth until 4 hours before death when she became semicomatose.

In reviewing this case in the light of the other reports on the use of peritoneal irrigation, we feel that we were perhaps a little too afraid of it with the result that the maximum benefits of this procedure were not obtained. The dangers of peritonitis and peritoneal irritation have been repeatedly emphasized, yet there is no case on record in which there were any ill effects as a result of this treatment. In many cases autopsies were obtained, and in one case laparotomy was performed some months after recovery at which time no evidence of peritonitis or adhesions was found. Any of the many antibiotics can be added to the irrigation solution to prevent infection. We did not employ heparin and did not believe that the flow was impaired by its omission. A continuous flow is probably effective in maintaining the patency of the outlet, as well as inhibiting bacterial growth. While there are individual variations, 2,000 c.c. is commonly tolerated in the peritoneal cavity during pneumoperitoneum and produced no discomfort in our case. This much is necessary to initiate outflow. Once outflow is established, the comfort of the patient is a reliable guide to the rate of inflow. We would caution against too much adjustment of the outflow mechanism. There is a tendency to cyclic flow and one should be certain that actual obstruction has occurred before changing the outlet drain. In most cases satisfactory flow will be resumed when the intra-abdominal pressure rises.

It was our intention, by the use of 5 per cent glucose rather than Tyrode's solution, to remove some fluid from the body and relieve the edema. We were successful in achieving this aim and several reports confirm this.<sup>7</sup> Substances other than urea and nonprotein nitrogen are excreted in the urine normally and there is no reason to be alarmed when they are detected in the peritoneal outflow fluid. If clinical electrolyte deficiency appears, it can be corrected by oral or intravenous medication with much more assurance of absorption.

### Comment

In reviewing the measures which are credited with restoring renal function in lower nephron nephrosis, we find that every method advocated has been used with success in several cases, but has failed in an equal or larger group of cases. One is forced to the conclusion that the condition terminates spontaneously in a period varying from a few hours to as long as two weeks, and is little influenced by any therapeutic measure.

The majority of methods of treatment are based on the assumption that some neural mechanism is involved in the production of anuria and are directed toward interrupting the nerve pathways to the kidney by spinal or splanchnic block, destruction of the nerve pathways by decortication, or by anesthetizing the injured cells by the injection of Pontocaine or procaine which localizes in the kidney in accordance with the Schwartzman reaction. Of these measures, decapsulation has the best record, but, unfortunately, is also the most formidable



procedure. In addition to interruption of the nerve pathways, decapsulation also relieve the intrarenal tension, thereby making possible the secretion of urine with a lower filtration pressure.

If there is any reason to believe that obstruction may be present, catheterization of the renal pelvis should be undertaken. The procedure is rather difficult for nonspecialists, but is relatively safe if one has ever passed sounds. Detailed instruction may be found in any textbook of urology.

X-ray therapy to the flanks has been reported as successful in three cases.<sup>8</sup> There is no experimental work which would give any clue as to why this method of treatment would give relief, but various types of physiotherapy, such as heat and diathermy, applied to the kidney region have been employed in many cases with no definite benefit.

In the very early stages, an attempt may be made to force the block by the administration of 10 per cent dextrose or other substances of high molecular weight. If any renal function remains, the dextrose will be excreted into the tubules where, being hypertonic, it attracts more fluid, which in turn promotes the excretion of more dextrose, etc., until a happy outcome is achieved. It must be emphasized that this treatment cannot be persisted in if there is not an immediate response, since the patient will be drowned in the excess fluid. Peripheral or pulmonary edema is a definite contraindication to such attempts.

In the original article by Bywaters and Beall, the authors speculate on the effect of adrenal cortical hormones on anuria. Since cortisone has been of value in many allergic and toxic conditions, it might be expected to exert some influence on the damaged tubules. Reflex anuria during the course of cortisone therapy has been reported. Apparently the drug did not prevent its development, but did not cause any harm, since a favorable outcome was noted. It would be relatively contraindicated in the latter stages when fluid retention and cardiac failure become manifest, but should not be harmful in the early period. It should be remembered that these patients often appear quite well during the first few days and one may be tempted to delay vigorous treatment until it is too late. Once deterioration begins, the patient grows rapidly worse until death.

There are various minor therapeutic measures which may ameliorate the azotemia to some extent, but cannot be considered as definitive treatment. Testosterone has been reported as delaying the rise in the nonprotein nitrogen, probably by promoting protein anabolism, thus converting the nitrogen to a form which can be stored.<sup>9</sup>

Cation exchange resins have some beneficial effects in reducing the blood potassium level.<sup>10</sup>

In addition to peritoneal irrigation, there are a number of measures which will reduce the nonprotein nitrogen. Our experience was limited to irrigation and we feel that it is adequate for this purpose if properly and vigorously applied. In general, the experience of others tends to confirm this view.

The earliest, and one of the simplest, methods of treatment of anuria is that of Bull,<sup>14</sup> the so-called conservative treatment. Essentially it consists of restriction of caloric intake to carbohydrates, limitation of fluid intake to exactly

the amount lost, and removal of nitrogen through a duodenal suction tube. The amount of nitrogenous waste products that can be removed by this method is rather limited.

One of the most formidable methods consists of the isolation of a loop of small intestine, the ends of which are brought out to the skin, for use as a dialyzing membrane by through-and-through irrigation. By this method, Twiss<sup>15</sup> achieved the incredible survival for 46 days of a patient who had a solitary kidney removed through error. In other cases, this method was less effective and one death has been reported from perforation of the perfused loop.

Exchange transfusion is very popular in Europe. By this technique a pint of the patient's blood is removed and replaced with a pint of blood having a normal nonprotein nitrogen, thus diluting the high N.P.N. to some extent. By continuing the process indefinitely, the N.P.N. may be kept somewhat lower than it would otherwise go. Unfortunately, it is often impossible to secure blood in the quantities necessary for this procedure, and in other cases the patient may be unable to tolerate the large number of transfusions necessary. In experimental work using dogs, it has been found that the kidneys of a normal animal are able to perform the excretion for both, without damage, when they are connected in cross circulation.<sup>11</sup> Circumstances might conceivably arise where this treatment could be applied to human beings.

The artificial kidney has been specifically developed to meet this problem, and several cases have been treated by its use with varying results. It is a rather cumbersome apparatus and is not readily available for general use. The technique is difficult, requiring continued vigilance and anticoagulants to prevent clogging of the machine. It has been suggested that the total dialyzing area of the peritoneum is much greater than that of this device, and some writers feel that it is inferior to irrigation.

Death in anuria is usually from pulmonary edema. As the N.P.N. rises, urea is secreted from all body surfaces in an effort to reach compensation. The net result of this in the lungs is to accelerate pulmonary edema. In addition, heart failure is brought on by direct poisoning from the accumulation of wastes, the hypertension, and the anemia, which is characteristic of uremia. Once pulmonary edema has developed there is little that can be done. The use of digitalis and positive-pressure oxygen are beneficial, but limited. They can be expected to extend survival by only one or two days at the most. In toxemia, where the blood pressure has been elevated for some time, heart failure and pulmonary edema may be anticipated earlier than with some of the other causes. Any pre-existing cardiac or renal disease will have the same effect.

In addition to the rise in the N.P.N., there is also a tendency toward salt depletion and potassium intoxication. The electrocardiogram is diagnostic in potassium disturbances and may be used as a guide to replacement therapy.<sup>12</sup> After renal function has been restored, there is an unselective excretion of both sodium and potassium through the damaged kidneys and death may occur from depletion of one or both of these elements. Convulsive seizures have been noted from sodium depletion in this phase. In addition, severe dehydration may occur. These problems, however, are dealt with easily, if anticipated.

In conclusion, we would like to suggest a treatment routine for these cases, based on the experience of others, and, to a limited extent, our own. The mortality in Lucke's series was estimated as 90 per cent, while present mortality is around 50 per cent. If cases of oliguria are included, the mortality is 25 per cent.

For purposes of treatment the disease is conveniently divided into stages:

1. *Prodromal Stage*.—Decreasing urinary output. Prompt restoration of blood volume and relief of shock. Correction of acidosis. Nontoxic diuretic measures such as 10 per cent glucose solution. Relief of obstructing lesion if present.

2. *First 24 to 48 Hours*.—Relief of obstructing lesion. Intravenous procaine or Pontocaine, spinal, paravertebral, or caudal anesthesia. Decortication. Ten per cent glucose (with caution).

3. *Maintenance Stage*.—Strict restriction of fluid intake. Reduction of N.P.N. by artificial kidney, peritoneal irrigation, or exchange transfusion. Continuous exchange through a healthy donor is theoretically possible.

4. *Terminal Stage*.—May develop any time after the fourth day. Careful observation and correction of electrolyte balance. Digitalization and oxygen at first evidence of pulmonary edema.

5. *Recovery Stage*.—Replacement of excess fluid and electrolyte loss.

### Summary

1. A case of crush syndrome following premature separation of the placenta is reported.

2. The available information on the etiology, mechanism, and treatment of this condition is reviewed.

3. Suggestions for treatment based on available case reports are given.

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## CIRCULATORY ADAPTATIONS TO BIRTH AND THEIR CLINICAL IMPLICATIONS\*

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THE topic which I have selected is one which interests me as a physiologist, but it has clinical overtones, as well. You will recognize, I believe, the clinical import of what is essentially a basic physiological story. And you will seize upon its lessons to apply them for a healthier and sounder start in life of children yet to be born.

If we are to discuss the circulatory changes that occur at birth, it is, you will agree, essential that we understand the hemodynamic character of the fetal circulation to begin with. I am sure that if you have thought of it—and I am certain of it if you have read about it—that you regard the fetal circulation as being like that of the adult, except for three things: (1) the ductus arteriosus which connects the pulmonary trunk with the descending aorta, (2) the foramen ovale which permits “fresh” blood returning from the placenta to pass to the left side of the heart and thence to the forepart of the fetus, and (3) the ductus venosus, a structure that permits blood to by-pass the fetal liver in returning from the placenta to the fetal heart.

These are essential features of the fetal circulation to comprehend. But they by no means reveal the peculiar or special physiological nature that marks it as different from that of the adult. There are, I should say, three more important respects in which the fetal circulation differs from that of the post-natal organism. These are: (a) the gradient of blood pressure throughout the system; (b) the speed and volume of blood moved through certain parts of the system, and (c) the pattern of nervous control of the fetal circulation. Let us examine these briefly.

*Pressure gradients:* In us, the level of blood pressure is high throughout the arteries, with the sharpest fall of pressure in the arterioles. The pressure in the capillaries is only a little above the pressure exerted by the osmotic pressure of the plasma proteins. *But this is not so in the main part of the circulatory system of the fetal sheep.* Here, a pressure drop probably occurs in placental arterioles, but in the capillary network of the placenta, including the fetal villi, pressure is high—about 40 to 50 mm. Hg. In the umbilical vein, the pressure is some 35 to 45 mm. Hg, a level higher than that of any other vein in the body.

I wrote the latter statement in December of 1953. At that time, it seemed to me to state well enough the essential characteristics of the pressure difference between the fetal and the adult circulations. Recent experiments which we have carried out in rhesus monkeys permit me to stress an additional and im-

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portant point of difference. When the uterus which contains a fetus contracts, intrauterine pressure increases. By catheterization of one of the fetal placental arteries (or veins) without entering the amnion (as is readily possible in the monkey), fetal blood pressure and heart rate can be determined throughout the cycle of uterine systole and diastole with the fetus entirely in utero. We have found, by doing this, that as intrauterine, or amniotic fluid, pressure rises when the uterus contracts the fetal blood pressure rises also and to the same extent. In short, when intrauterine pressure in the monkey rises from a resting level of 5 up to 45 mm. Hg, fetal blood pressure in the monkey rises from a level of 35 up to 75 mm. Hg. The fetus maintains, therefore, a relatively constant differential of pressure between the inside and the outside of its vascular system.\* This seems at first sight to be an extreme degree of fluctuation of pressure for the fetus, as indeed it is. The fetal heart must develop more pressure to eject the blood as a result of a strong uterine contraction. Nevertheless, the pressure equilibrium between the inside and outside of small fetal blood vessels remains in a state of pressure equilibrium. This mechanism must assure a degree of stability in the fetal tissues and placenta with respect to fluid exchange without which the fetus would suffer.

Returning now to the blood pressure in the umbilical vein, how do we know that it is high, approaching arterial pressure? We know it from direct measurements. Fetal blood pressure in the umbilical vein is difficult to measure accurately, for the vein will collapse if one is in the least careless. The reason for a high umbilical vein pressure is an interesting one. The placenta is drained by the umbilical vein to the inferior vena cava. It may go by way of the ductus venosus, or by way of the hepatic circulation. What regulates the route it will take there?

There is a belief stated by Barcroft that the ductus venosus is always open during fetal life, and that it closes after birth. But what are the facts? Radiographs taken at 3 per second show that a sphincter mechanism at the beginning of the ductus venosus is a sphincter, and that it can close within the space of a third of a second. Our study of the embryology of this structure shows that it begins to form in the 5 mm. embryo, and it is definitely formed by twelve weeks, and complete by the twentieth week of fetal life. It is innervated by the vagus nerve.

When we examined this structure by cineradiographs, taken at 25 pictures a second, we found that it is almost closed when venous return is normal; partly open when venous return is less, and fully open when venous return is nil. It is premature to say what this means. I suspect, however, that when we know the answer for sure, we will be in a position to say that the ductus venosus closes to divert to the liver blood returning in high volume in order to prevent sudden overloading of the fetal heart. This could well occur when the uterus contracts.

What are the consequences of a high venous pressure in the umbilical vein? We have seen that it maintains a high pressure throughout the cord and placenta. This maintains a vis-a-tergo in the cord. *It is, therefore, during life,*

\*This is with rhythmic uterine contractions. Induced and sustained contractions give rise to circulatory responses in the fetus which cause the blood pressure to increase more, or less, than this amount.

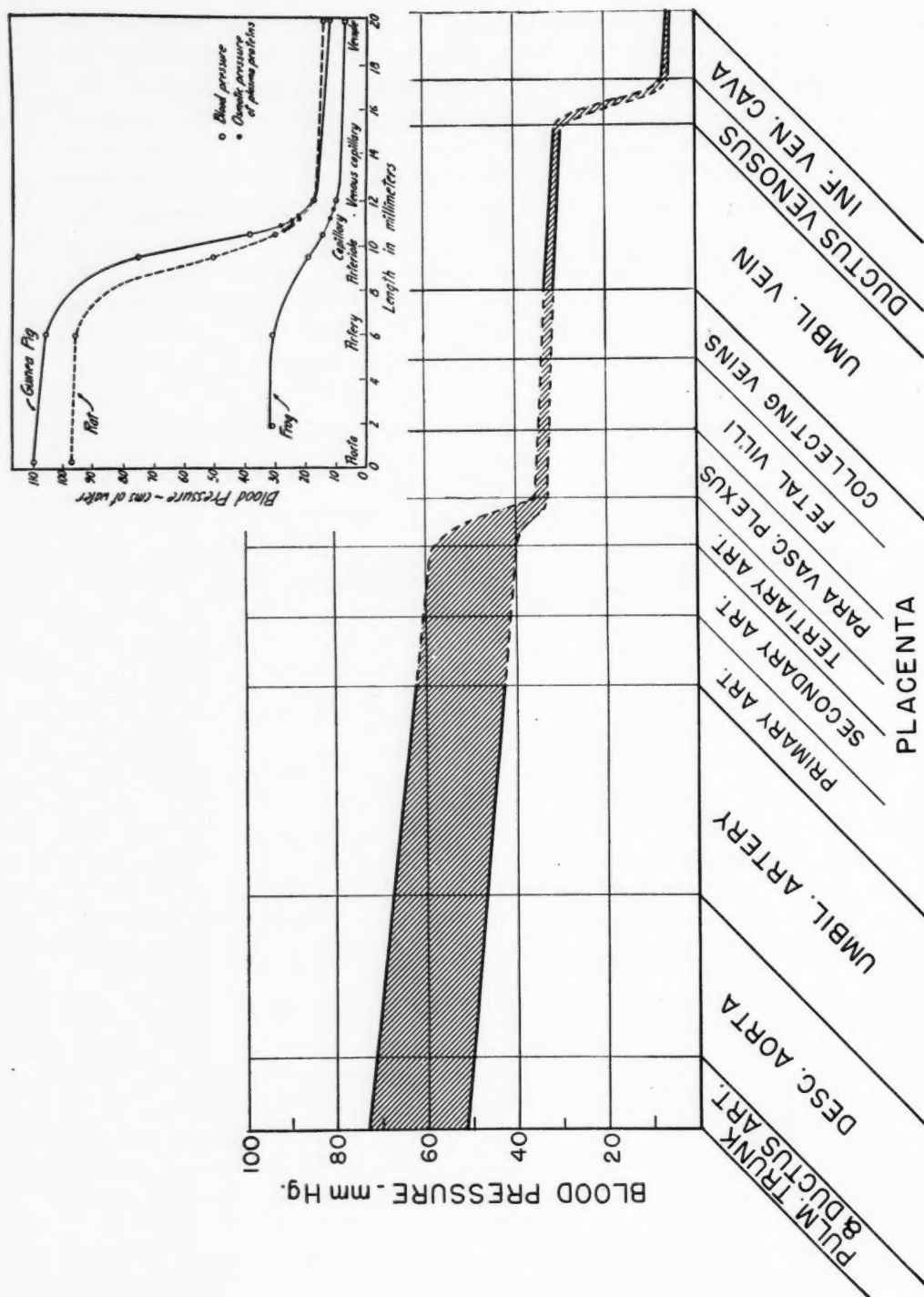


Fig. 1.—(Inset with Fig. 2.) Graph showing greatest fall in blood pressure in the arterioles of 3 species of animals. Note the low venous pressure level. (From Landis, *Physiol. Rev.* 14: 404, 1934.)

Fig. 2.—Graph of blood pressure levels in the fetal lamb. Note high umbilical vein pressure level in the fetal lamb, and drop in pressure between there and the inferior vena cava.

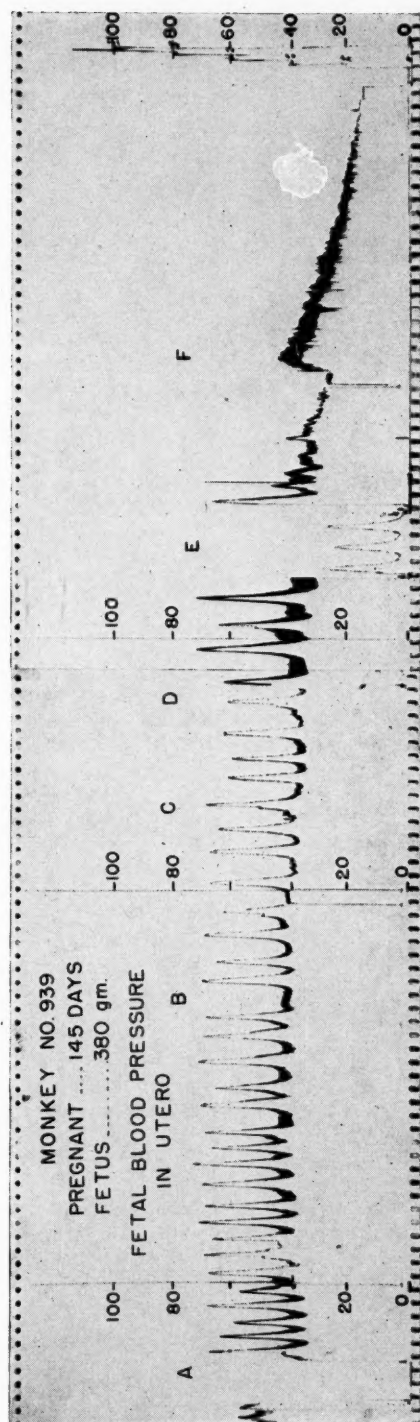


Fig. 3.—Fetal blood pressure, recorded with monkey fetus in utero and membranes intact. Catheterization of interplacental artery as it runs between membranes and uterus from primary to secondary placenta. A, Sample of fetal blood drawn. B, Begin intravenous glucose to mother. C, 1 c.c. Pentothal to mother. D, Sample of fetal blood drawn. E, Amniotic fluid pressure (mother died). F, 0.12 mg. Adrenalin (fetus died).

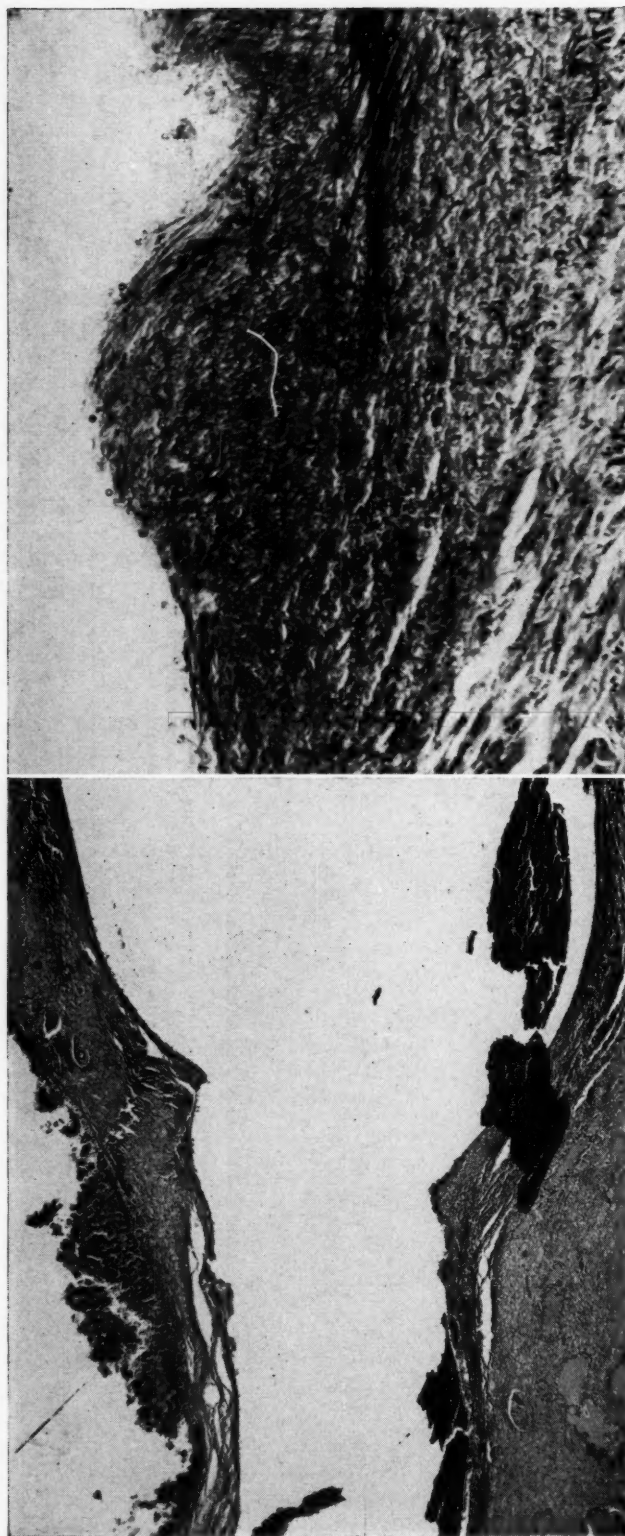


Fig. 4.

Fig. 4.—Longitudinal section of human ductus venosus (left) and end of umbilical vein (right), showing sphincter of the ductus venosus between the two. Fetus aged 12 weeks. ( $\times 30$ ; reduced  $\frac{1}{10}$ .) (From original of Fig. 5, Chacko and Reynolds: Anat. Rec. 115: 151, 1953.)

Fig. 5.

Fig. 5.—Detail of sphincter of ductus venosus. Elastic tissue stain (Weigert). ( $\times 200$ ; reduced  $\frac{1}{10}$ .) (From original of Fig. 6, Chacko and Reynolds: Anat. Rec. 115: 151, 1953.)



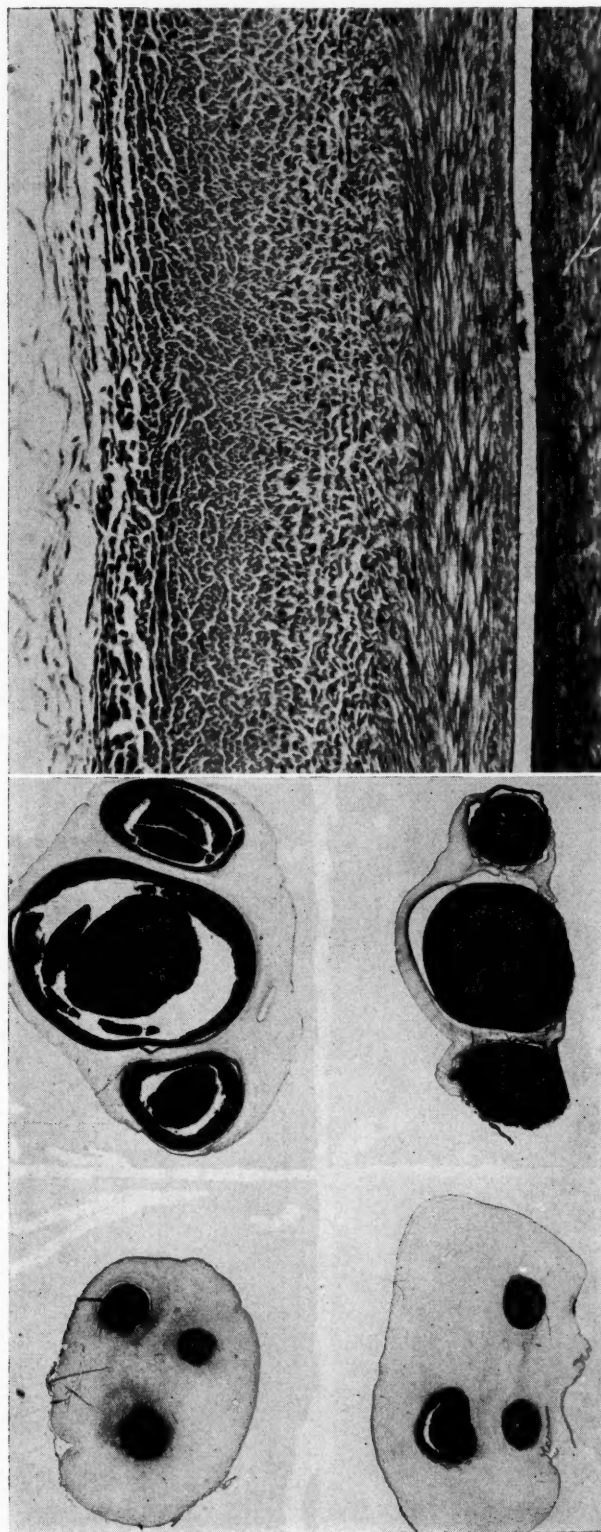


Fig.

Fig. 6.—Cross sections of umbilical arteries, nondistended on left, and normally distended on right. Note sizes of vessels and less Wharton's jelly. (From original of Fig. 1, Reynolds: Anat. Rec. 113: 365, 1952.)

Fig. 7.—Longitudinal section of a contracted umbilical artery. Lumen is clear strip. Note arrangement of muscles and thick wall. ( $\times 60$ ; reduced  $\frac{1}{10}$ .) (From Chacko and Reynolds: Contrib. Embryol. 35: 135, 1954.)

Fig. 7.



Fig. 8.

Fig. 8.—Same as Fig. 6 except that artery is dilated, as when carrying blood. Note elastic lamina. Wall is  $\frac{1}{6}$  to  $\frac{1}{4}$  mm. thickness. ( $\times 500$ ; reduced  $\frac{1}{10}$ .) (From Chacko and Reynolds: Contrib. Embryol. 35: 135, 1954.)



Fig. 9.

Fig. 9.—Smooth muscle in a distended umbilical vein, showing the interlacing and syncytial character, to resist further distention (distention and elongated). (From Chacko and Reynolds: Contrib. Embryol. 35: 135, 1954.)

*an erectile structure!* This is shown to be so in properly fixed sections, made when the cord is fixed distended as when the vessels are carrying blood. What is gained by this? Obviously, distention keeps the arteries and veins large. Therefore, the pressure drop along them resulting from frictional resistance will be slight and, at the same time, the volume flow of blood can be large. This seems, therefore, to be the real crux of the difference in the hemodynamic nature of the fetal and postnatal circulations.

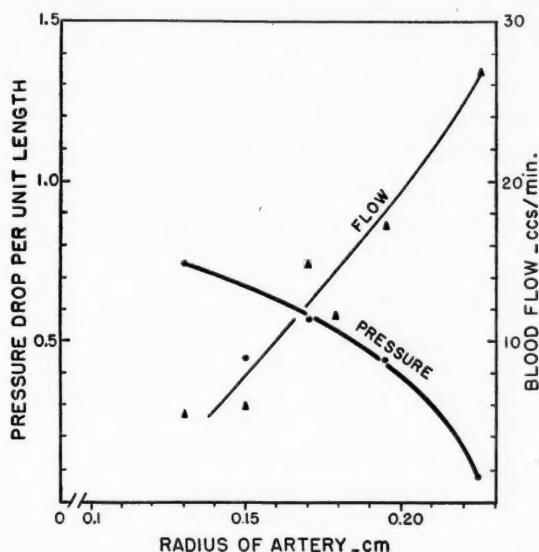


Fig. 10.—Significance of dilation of umbilical artery on flow characteristics. Bottom, radius of artery; left, pressure drop (centimeters of water) per centimeter length of artery; right, flow in artery (milliliters per second). (Based on Reynolds, Light, Ardran, and Prichard: Bull. Johns Hopkins Hosp. 91: 83, 1952.)

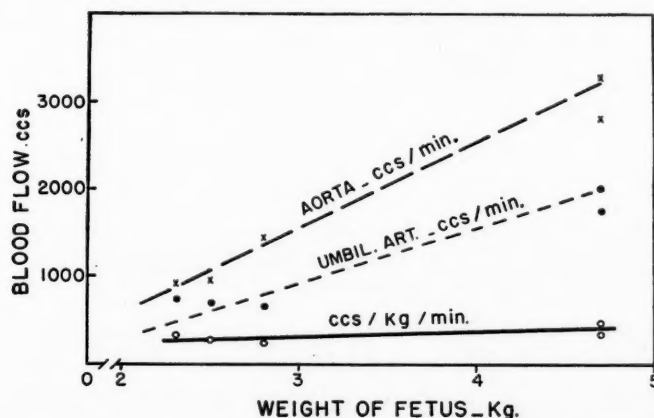


Fig. 11.—Flow of blood in the aorta and umbilical cord of the sheep as a function of fetal weight. Cord flow is two-thirds the flow in the descending aorta, but the flow (cubic centimeters per kilogram per minute) is constant. This shows that fetal cardiac output (not the length or twists in a cord) normally determines the flow between placenta and fetus.

I turn now to the second physiological difference between the two circulations, namely, that of the volume flow of blood throughout the organism. The cardiac output of the fetus is unique; it passes mostly (75 per cent) to the

caudal end of the fetus, because of the confluence of the streams from the right and left sides of the heart below the ductus arteriosus. About 15 per cent goes to the head, and 10 per cent to the fetal lungs. How much goes to the placenta?

Regardless of the age of the fetus, about two-thirds of the aortic flow, or 50 per cent of the cardiac output, passes to the placenta. Since this is a fixed ratio of the aortic flow, it means that the determining factor in placental blood flow is not the length or tortuosity of the cord, but rather the fetal cardiac output. This is because the caliber of the placental blood vessels is large enough not to be a major factor in the dissipation of hemodynamic energy through friction. What more effective arrangement could Nature devise than that the fetal heart provide for its own welfare?

COMPARISON OF BRADYCARDIA RESPONSES TO  
ARTERIAL AND VENOUS OCCLUSION

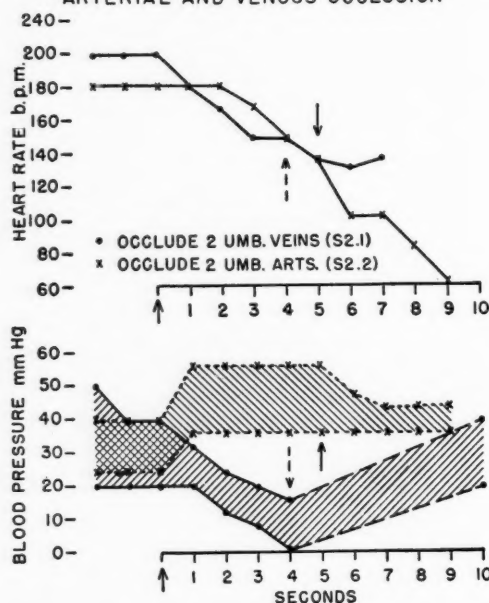


Fig. 12.—Reflex fetal bradycardia in the sheep resulting from temporary occlusion of the umbilical arteries (crosses) and veins (dots). Occlusion released at arrows. Graph below shows that effect is not dependent on a rise in arterial blood pressure, since with venous occlusion there was a fall in pressure and bradycardia. (From Reynolds: *Am. J. Physiol.* 176: 169, 1954.)

There is another feature of the fetal circulation I must stress. It is this: the velocity of blood flow in the fetus is fastest in the descending aorta. A large volume of fast-moving blood hits the umbilical arteries like the bull's-eye of a target. These arteries could not be more advantageously placed to utilize to the full the advantage of energy derived from a large volume of fast-moving blood. The slowest blood flow is to the head end of the fetus.

Since most of you are obstetricians, I must mention the fourth and final important difference between the fetal and postnatal circulations. I refer to



the reflex control of the fetal heart. I shall speak first of the mechanism of bradycardia with fetal distress. This is important obstetrically.

Within seconds after experimental occlusion of the umbilical cord, the heart slows down. Barcroft says this is due to depressor reflexes resulting from an elevation of pressure in the aorta. When I examined this more closely, I found it to be only a partial answer. When the umbilical arteries alone are occluded, the pressure rises, the heart slows, and the response is abolished by vagotomy. But so, too, when the umbilical veins are occluded, the heart slows and there is a *fall* in blood pressure. This effect is abolished by vagotomy.

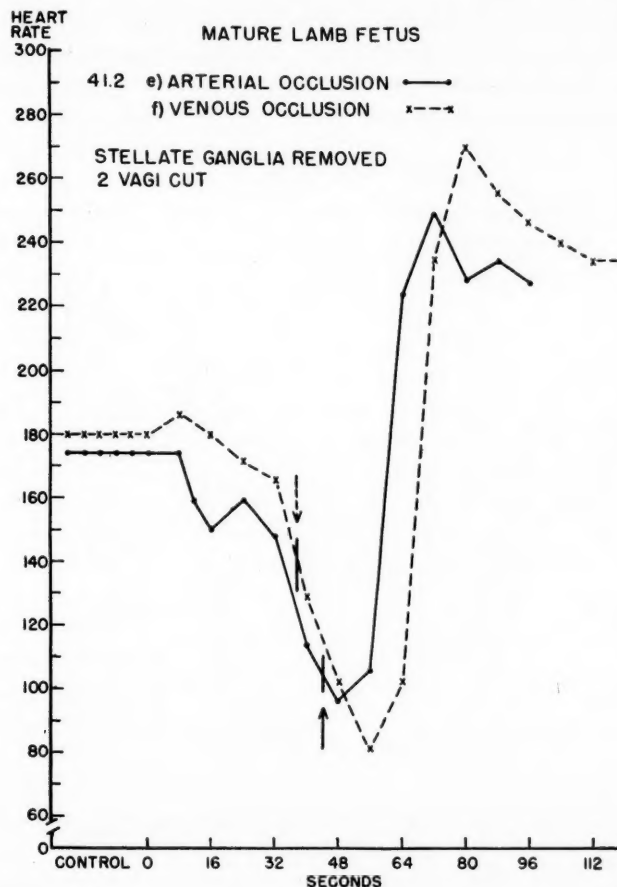


Fig. 13.—Tachycardia following anoxic bradycardia in lamb fetus with a denervated heart when umbilical arteries (solid line) and umbilical veins (broken line) are occluded. (From Reynolds: Am. J. Physiol. 176: 162, 1954.)

Clearly, fetal bradycardia reveals reflex action arising from the large veins of the fetus, possibly in the vicinity of the umbilical recess or the effect of anoxia on medullary centers. This, then, is the first lesson I have to teach you about the control of the fetal heart.

The second lesson is of interest to those who are physiologically minded. It is that, in the fetus at rest, *there is no vagal tone*. For example, when the vagus nerves are cut, the heart rate *slows down*, not speeds up, as in postnatal

animals. Yet, when the peripheral ends of the cut vagi are stimulated, the heart stops, so the fetal vagus is inhibitory. Can vagal tone be induced in the fetus? Yes, it can. For example, with mild circulatory distress, the heart rate slows down but it does not recover upon release of the circulation. Thus, we induce vagal tone in response to mild stress. In the resting fetus, therefore, the nerve connections are intact—the wires are up, the connections are made, but the line is *not* busy.

The next lesson I have to tell you is important physiologically and obstetrically. It has to do with the response of the heart to severe circulatory distress. I studied this in sheep fetuses with completely denervated hearts. The vagi were cut, and all sympathetic nerves to the heart were removed. Upon inducing anoxic slowing of the fetal heart, the heartbeat becomes very fast indeed on recovery, nearly 300 beats per minute. This tachycardia lasts for a long time. Why should this be so?

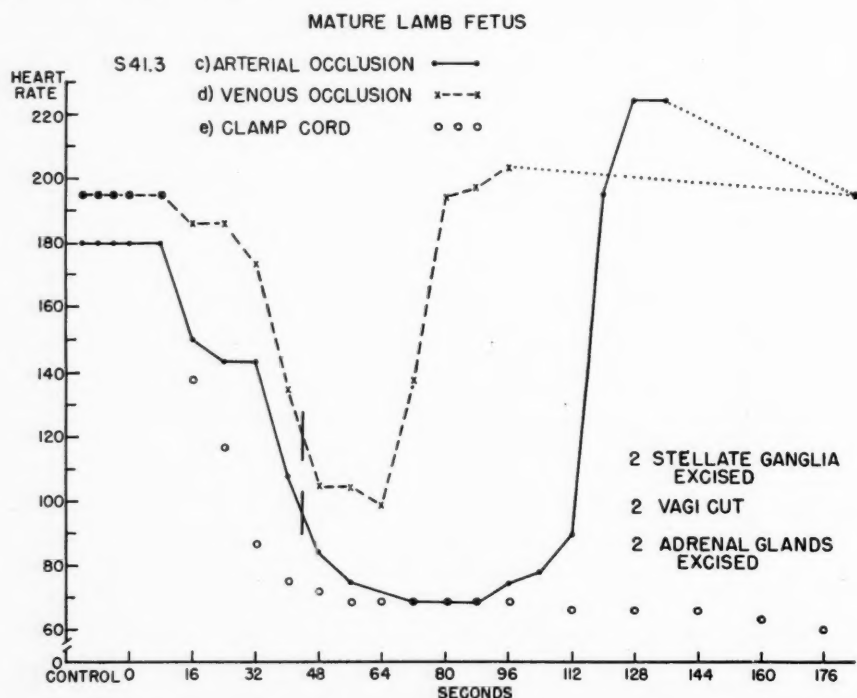


Fig. 14.—Abolishment of fetal tachycardia following anoxic bradycardia (with the heart denervated) by removal of the fetal adrenal glands. Bradycardia is (a) first, reflex, mediated over the vagal nerves; (b) anoxic, by direct cardiac action; and tachycardia in response to extreme distress is from endogenous, fetal adrenaline. (From Reynolds: *Am. J. Physiol.* 176: 162, 1954.)

The reason is that the cardio-accelerating stimulus comes from mass stimulation of the sympathetic system, and production of endogenous adrenaline. Tachycardia does not occur when the adrenal glands are removed!

We see, therefore, that when tachycardia follows bradycardia it is a very unfavorable obstetrical sign. It means that the fetus already has been pushed to the last line of its physiological reserves.

Surveying what we have just said, we see that the fetal circulation is very different from that of the postnatal animal. The circulatory system is so de-

signed and it so operates that it serves the primary function of supporting the exchange of blood between the placenta and fetus. The cord is erectile to keep it from collapsing and so to minimize frictional resistance and loss of energy by blood as it flows; there is a blood reservoir in the fetal liver to permit adjustment of the conceptus to its inevitable uterine environment; the reflex control of the heart is such that it is relatively insensitive to the milder sorts of stresses and strains, but it possesses a very potent last line of defense. We have seen that the blood moves fastest and in greatest abundance toward the umbilical arteries, and that it moves slowly and in small amount to the head and lungs of the fetus. Clearly, these conditions are subservient to the need for placental exchange, as may well be imagined. Nature contrives, nevertheless, to supply the head of the fetus with freshly oxygenated blood by shunting some through the foramen ovale from the right side of the heart to the left from whence it passes up the aorta to the head of the organism.

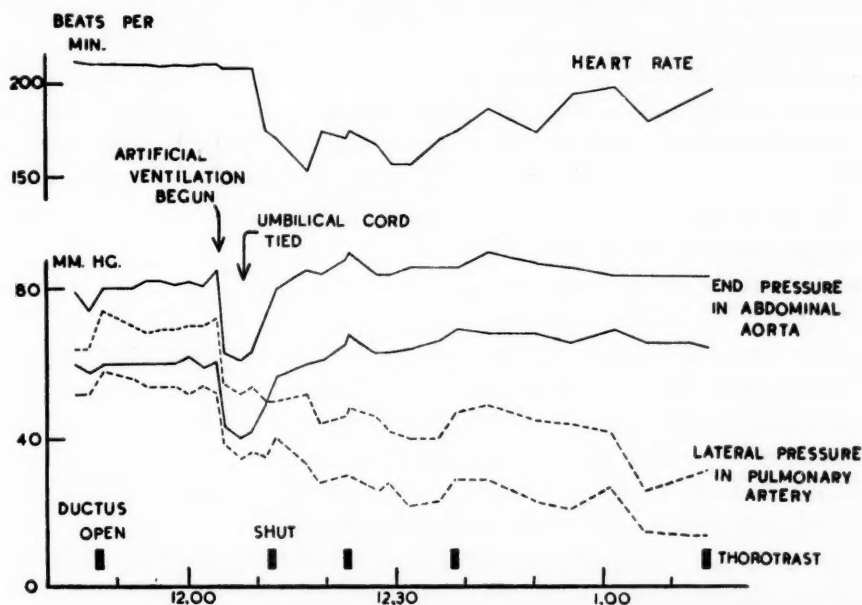


Fig. 15.—Effect of aeration of fetal sheep lung on fetal systemic blood pressure, pulmonary arterial blood pressure, and fetal heart rate. By cineangiography, ductus arteriosus was open or shut as indicated for Thorotrast. See text for discussion. (From Ardran, Dawes, Prichard, Reynolds, and Wyatt: *J. Physiol.* 118: 12, 1952, Cambridge University Press.)

We turn now to consider *what* changes transpire in the circulation at birth; *when* they transpire; and *why* they transpire. Let us look first into changes at birth. I would mention as a corollary one other feature. This is upon the work of a number of us in 1951 at the Nuffield Institute for Medical Research. It is characterized particularly on the one hand by the fact that we took x-ray movies at a speed of 25 pictures a second, and on the other by the fact that, for the first time, we recorded blood pressure continuously in the pulmonary trunk and the descending aorta. The x-ray movies which you will see show each photograph of the same shot of opaque medium repeated five times.

The striking features of this movie are clear, I believe. The change-over from the fetal to the adult circulation is sudden—there is a sudden increase in the

speed and quantity of blood flowing into the lungs. As the lungs distend, they fill with blood, and momentarily there is reduced venous return of blood to the left side of the heart. Consequently, systemic blood pressure falls. Since pulmonary arterial blood pressure falls because pulmonary peripheral resistance decreases upon aeration, the initial moments after birth are characterized by an extensive fall in blood pressure throughout the entire animal. This has been found to be true in the human being by Dr. Monfort, of Brooklyn, N. Y., who measured blood pressure by the flush method in a delivered fetal arm and then repeatedly during and after delivery. This observation was anticipated by only one worker before us, Schultze, of Germany, in 1871. No one believed him.

At the time of low blood pressure, the ductus arteriosus closes. Why? Clearly, it does so because the props supporting it are removed when the blood pressure falls, first as in the umbilical arteries. Reflexes are not essential, since a denervated ductus arteriosus will close. Oxygen is not necessary, for it will close if the lungs are distended with nitrogen. Finally, it *will* close in the face of an elevated blood pressure, as during asphyxia, when the contractile power of the muscle in the ductus is stimulated, as other vascular structures are, by carbon dioxide. Clearly, an open or a closed ductus is the result of a preponderance of force in one direction or the other, the contractile stress of the ductus opposing the distending force of the blood pressure. This is a hemodynamic concept of ductus closure.

We see, therefore, the *what*, the *when*, and the *why* of postnatal circulatory changes at birth. I would mention as a corollary one other feature. This is that, as the pulmonary circulation speeds up, so also does that to the head, and that to the placenta becomes, of course, zero. In short, the tables are turned, in one sense, for the circulation is now fast to where it was slow, and vice versa. In each case, it is the organ of respiration that receives the fast and abundant circulation of blood. Clearly, anything which prevents operation of this principle at all times works against the welfare of the baby.

And now, what practical lessons may we learn? I shall describe briefly a number of points which should now be clear to you.

First, let us consider the capacity of the fetus to respond to stress. This depends, we have seen, on an adequate sympathetic response mechanism. There are some workers who advocate the use of adrenolytic substances to shorten labor and to soften the cervix during dilatation. I would say to this, the adrenolytics used so far are oxytocics, despite claims to the contrary, and they may well contribute to delayed postnatal pathology, particularly to subarachnoid hemorrhage, associated with convulsions, coma, and death a day after birth. I have seen this.

The second lesson we learn pertains to the fall in blood pressure which occurs postnatally. The pulmonary vascular capacity increases on aeration of the lungs. This calls for more blood to fill the system. This ought to come from the placenta, but does it always, in well-managed clinics? The present practice is "to wait" before clamping the cord. To wait for what? The cord



to stop pulsating? This merely means the blood pressure in it is low enough to allow the vessels to constrict. Wait for blood to run into the baby? This is well and good, provided circumstances permit it. I saw data by Dr. Mary Gunther of University College, London, showing that a baby placed on scales but still attached to a placenta in utero may be made to lose weight by raising the baby above the level of the placenta; it will gain weight—30 to 100 grams—by holding it below the level of the placenta. Gravity, therefore, determines the direction of flow. This conclusion has been amply supported by Dr. Duckman, of Brooklyn, who adds the fact that babies who gain this added blood do better in the perinatal period than those who do not. This results from increased blood volume rather more than from increasing the iron reserves of the baby. In any case, it is bad practice to put the baby on the mother's abdomen, with the mother in the Trendelenburg position, and wait for the cord to stop pulsating. Unless the uterus happens to be contracted at the moment of elevation of the baby for cutting the cord, blood runs into the placenta.

I have not told you of our observations on the forces of blood flow in the umbilical cord. If I had, I would seem less didactic to you than I must, speaking briefly on the subject. I assure you, however, that the conclusions which I have given you are amply supported by a number of facts which, for the sake of simplicity, I have refrained from telling you today.

## INCIDENCE OF PREGNANCY DURING LACTATION IN 500 CASES

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THE purpose of this study, conducted at the Catholic Maternity Institute, Santa Fe, New Mexico, in the spring of 1953, was to determine the exact time and occurrence of pregnancy during the lactating period in 500 cases. It was made in particular in order to ascertain to what extent or degree breast feeding protects the mother, as a natural means, to regain her health and strength, by the adequate spacing of children, before assuming another pregnancy.

This subject has been a matter of speculation among lay and professional persons from time immemorial. Rice,<sup>14</sup> in discussing the physiological and psychological advantages of breast feeding for both mother and baby, adds another function of lactation when he states that in most cases it constitutes a natural spacer of children. He adds, however, that today, with the increased use of supplementary feedings during lactation, the procedure of breast feeding no longer offers the same degree of protection against too frequent pregnancy. Udesky<sup>19</sup> bears this fact out, in his study on the occurrence of ovulation during lactation. He found that there was an increased incidence of ovulation as soon as the weaning process went into effect, or when supplementary feedings were started to replace breast feedings.

The maternity service in which the study was made was chosen for two reasons: (1) The large number of mothers who breast fed their babies, and continued lactation as long as possible. (2) The policy of this service, to encourage and maintain breast feeding as long as possible by individual and group instruction in mothers' classes.

The information secured in this study was obtained from the patient's antenatal history which includes the expected date of confinement, length of breast feeding of the last baby, and also includes a history of previous pregnancies with date of birth, and length of breast feeding for each. The date of conception was estimated by using the date of the last menstrual period, the weeks of gestation, the expected date of confinement, or the date of actual delivery. In a small percentage of cases, it was possible to confirm some of this information from the patients in their clinic visits or during the course of a regular home visit by one of the nurses.

### Review of Literature and Related Studies

Studies made by Pinard<sup>13</sup> in 1909 and Ehrenfest<sup>6</sup> in 1915 analyze the reappearance of menstruation after childbirth. Peckham<sup>12</sup> in 1934 studied the incidence of menstruation and percentage of pregnancies noted during lactation, but did not indicate the exact time and occurrence of these preg-

nancies, and limited his study to one year after delivery. He found that 30.38 per cent of the patients became pregnant again during the first year after delivery. Of this series, 35.75 per cent of the white patients and 46.98 per cent of the Negro patients were still lactating at the time of conception. Menstruation recurred before the cessation of lactation in 71.45 per cent of the cases, and in more than one-third of these preceded it by seven or more months. The menses were usually established within two months, when lactation ceased first. Half of the patients who were lactating at the time of conception had menstruated four or more times before the second pregnancy occurred, and about one-tenth of the total number conceived without having a menstrual period. Menstruation recurred more frequently in those patients who continued breast feeding for a longer period of time. Thus, in those patients who could breast feed only one month, menstruation had recurred in less than 1 per cent, while the figure for two months was 32.73 per cent, and by the end of a year, 81.40 per cent. It is obvious that of the 69.62 per cent of patients who did not conceive within the twelve-month period, there were a good number who were still lactating.

In 1937, Kurzrok, Lass, and Smelser<sup>9</sup> found that 42 to 63 per cent of the lactating women who bled at fairly regular intervals, or had menstrual symptoms, were found to have anovulatory or sterile cycles. Udesky,<sup>19</sup> in 1950, found that the suppression of the ovarian cycle is almost complete during lactation amenorrhea. When menstruation occurs during lactation, the suppression of the ovarian cycle is gradually lifted. In this study, ovulation occurred in the first postpartum period in 14 per cent, while in over 28 per cent ovulation occurred after three or more periods. When ovulation did occur, it was usually in the patient in whom lactation had been present for three or four months at least. Since the presence of ovulation indicates only a potential for pregnancy, however, this study did not give the actual time and occurrence of pregnancy during lactation, nor did I find any other study which gave this information.

#### **Presentation, Analysis, and Interpretation of Data**

A total of 189 mothers' case histories were canvassed in the maternity service in order to secure the desired 500 pregnancies. Of these 189, it was necessary to exclude 41 total case histories for the following reasons: incomplete history, no menstrual history, irregular menstrual history, uncertain history, no history of breast feeding, excessive length between pregnancies, illegitimacy, venereal disease and other physical abnormalities or conditions that would probably indicate a deviation from normal during breast feeding and immediately after.

Of the 148 mothers selected for the study, with a total of 895 pregnancies, it was necessary to exclude almost one-half of the pregnancies, or 395, for the following reasons: abortions, stillbirths, death of the infant shortly after birth, no breast feeding, illegitimate births before or during marriage, incomplete history as to date of birth or length of breast feeding, and irregular menstrual history for the specific pregnancies excluded. The number of mothers included in the study with the total number of pregnancies according to gravidity are shown in Table I. Primiparas are necessarily excluded.

In trying to secure the desired number of pregnancies, an attempt was made to secure as many as possible from the active case load of patients in the current year. Almost half were secured in 1953; the remainder were selected from the previous years. Criteria for the selection of cases from previous years were: (1) greater length of breast feeding; (2) greater num-

ber of pregnancies for each mother. Of the 148 patients selected, 73 were currently using the service in 1953. Of the others, 49 patients used the service in 1952, 11 in 1951, 6 in 1950, 2 in 1949, 1 in 1948, 4 in 1947, 1 in 1946, and 1 in 1945. These figures are shown in Table II.

TABLE I. CASE LOAD CANVASSED

GRAVIDA	NUMBER OF MOTHERS	NUMBER OF PREGNANCIES	PER CENT OF 148
ii	17	34	11.49
iii	18	54	12.16
iv	27	108	18.24
v	18	90	12.16
vi	15	90	10.14
vii	9	63	6.08
viii	9	72	6.08
ix	6	54	4.05
x	9	90	6.08
xi	8	88	5.40
xii	7	84	4.73
xiii	3	39	2.03
xiv	1	14	.68
xv	1	15	.68
Total	148	895	100.00

TABLE II. LAST YEAR MATERNITY SERVICE USED BY PATIENTS

YEAR	NUMBER OF PATIENTS	PER CENT OF 148
1953	73	49.32
1952	49	33.11
1951	11	7.43
1950	6	4.05
1949	2	1.35
1948	1	.68
1947	4	2.70
1946	1	.68
1945	1	.68
Total	148	100.00

#### *Menstrual History of Patients.—*

To avoid discrepancy in calculating the date of conception, it was important to exclude all cases of irregular menstrual history. Criteria for selection of cases with regular menstrual history was chosen from Beck<sup>3</sup>: "Regardless of the different frequencies in different women, the length of each woman's cycle is within a few days of the average length of all her cycles. . . . Most women flow from 3 to 5 days but a longer or shorter duration is not uncommon." Beck, in relating menstruation to ovulation, fertilization, and implantation, tells us that the ovum leaves the ovary about 14 days before the end of the cycle; that is, before the next period is expected, and that ovulation is therefore calculated with reference to the next anticipated menstruation.

TABLE III. MENSTRUAL HISTORY

	NUMBER OF CASES	PER CENT OF 148
1. 26-30 day cycle: 3-6 days in length	141	95.27
2. 23-30 day cycle: 3-5 days in length	3	2.03
3. 24-25 day cycle: 4-5 days in length	2	1.35
4. 32-34 day cycle: 4-5 days in length	2	1.35
Total	148	100.00



TABLE IV. INTERVALS BETWEEN BIRTHS IN RELATION TO NUMBER OF PREGNANCIES (500 CASES)

INTERVAL	NUMBER OF PREGNANCIES														TOTAL	
	2	3	4	5	6	7	8	9	10	11	12	13	14	NO.	PER CENT OF 500	
10-14 months	25	16	20	10	6	9	7	6	3		2	1		105	21.0	
15-19 months	33	27	15	15	8	3	2	3	4	1		1	1	113	22.6	
20-24 months	30	28	13	16	10	7	6	6	4	5	5	2		132	26.4	
25-29 months	13	9	16	11	8	3	8	3		1				72	14.4	
30-34 months	6	9	7	2	2	2	2	2	1	2				35	7.0	
35-39 months	3	2	4	3	5	2			1		1			21	4.2	
40-44 months	2	2		1	2	3	1		2					13	2.6	
45-49 months	2	2			1									5	1.0	
50 (and over)	1				2				1					4	0.8	
Total	115	95	75	58	44	29	26	20	16	9	8	4	1	500	100.00	
Per cent of 500	23	19	15	11.6	8.8	5.8	5.2	4.	3.2	1.8	1.6	0.8	0.2		100.00	

\*The 10 to 24 month interval constitutes 70 per cent of the total number of cases.

EASTMAN'S TABLE III\*  
DISTRIBUTION OF 5,158 OBSTETRIC CASES IN FOUR MAIN GROUPS ACCORDING TO WHETHER  
INTERVAL SINCE LAST VIABLE DELIVERY WAS VERY BRIEF, BRIEF,  
MODERATE OR LONG

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	PER CENT OF TOTAL
Very Brief—Less than 12 months	115	2.2†
Brief—13 to 24 months	1,347	26.1†
Moderate—25 to 48 months	2,191	42.5†
Long—More than 48 months	1,505	29.2†
Total	5,158	100.0

\*From Eastman.<sup>5</sup>

†The 10 to 24 month interval constitutes 28.3 per cent of the total number of cases.  
‡The 25 to more than 48 month interval constitutes 71.7 per cent of the total number of cases.

There was a slight variation among the cases selected for this study. The group was divided into four classes, each class presenting a homogeneous pattern as far as regularity between periods and length of periods is concerned. Most of the cases fell into the first class of a 26 to 30 day cycle, with length of period from 3 to 6 days; 141 of the 148 patients were in this first group. The remaining figures are shown in Table III.

*Intervals Between Births in Relation to Number of Pregnancies.—*

Among the 500 pregnancies in this study, it was important to note that in 70 per cent, or almost three-fourths, the interval between births was between 20 to 24 months or under two years. In 105 pregnancies, the interval was between 10 and 14 months; in 113 pregnancies, the interval was 15 to 19 months; in 132 pregnancies (the largest number), the interval was 20 to 24 months; in 72 pregnancies, the interval was 25 to 29 months; in 35 pregnancies, the interval was 30 to 34 months. The remaining figures are shown in Table IV.

The importance of these figures is indicated in Eastman's<sup>5</sup> study of 5,158 multiparas. This study indicates that the results for mother and baby are much more favorable when the interval between births is from 12 to 24 months, rather than a longer interval. Eastman states that about one-half of the private patients had intervals between 25 and 48 months between births, indicating, as he says, that this class of patients *spaced their children intentionally*. Comparison of Table III of Eastman's study with Table IV of this study is noteworthy.

In considering the months available for conception during the first year after delivery, Eastman accounts also for the lactation factor, in addition to prematurity and abortion, when he says: "But we have reckoned thus far without considering the factor of lactation which, of course, suppresses ovulation and tends to produce sterility."

TABLE V. NUMBER OF MONTHS INFANTS BREAST FED

NUMBER OF MONTHS INFANTS BREAST FED	NUMBER OF CASES	PER CENT OF 500
Less than 1	13	2.6
1	37	7.4
2	39	7.8
3	66	13.2
4	18	3.6
5	20	4.0
6	24	4.8
7	7	1.4
8	21	4.2
9	71	14.2
10	15	3.0
11	16	3.2
12	111	22.2
13	17	3.4
14	4	0.8
15	6	1.2
16	2	0.4
18	9	1.8
19	2	0.4
24	1	0.2
36	1	0.2
Total	500	100.00

*Length of Time Infants Breast Fed in Number of Months.—*

Of the 500 pregnancies, the greater number, 111 babies were breast fed for 12 months; 71 were breast fed for 9 months; 66 were breast fed for 3 months. In the cumulative series; 173 breast fed from 1 to 4 months; 143 breast fed from 5 to 9 months; 163 breast fed from 10 to 14 months; 19 from 15 to 19 months, while one was breast fed for 24 months, and another for 36 months. These figures are shown in Table V.

**Incidence of Pregnancy During Lactation**

Among the 500 pregnancies studied, there were 46 cases in which a pregnancy occurred during lactation. This was 9.2 per cent of 500 pregnancies. Of these 46 cases noted, 3 cases occurred in the fourth month of breast feeding; one case occurred in the fifth month of breast feeding; 3 cases occurred in the sixth month of breast feeding; 4 cases occurred in the seventh month; 7 cases occurred in the eighth month; 7 cases occurred in the ninth month; 5 cases occurred in the tenth month; 5 cases occurred in the eleventh month; 4 cases occurred in the twelfth month; 5 cases occurred in the thirteenth month; one case occurred in the fourteenth month and one in the sixteenth month. These figures are shown in Table VI, and graphically demonstrated in Figs. 1 and 2.

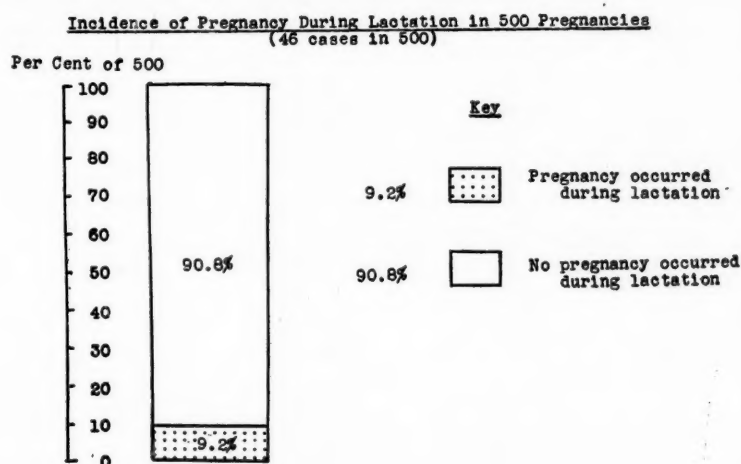


Fig. 1.

*Time Breast Feeding Ended After Pregnancy Occurred.—*

In the 46 cases of pregnancy during lactation, it was noted that 10 cases occurred within the last month of breast feeding; in 11 cases, breast feeding stopped one month after pregnancy occurred; in 12 cases, breast feeding stopped two months after pregnancy occurred; in 7 cases, breast feeding stopped three months after pregnancy occurred; in two cases, breast feeding stopped four months after pregnancy occurred; in 3 cases breast feeding stopped five months after pregnancy occurred; and in one case, breast feeding stopped six months after pregnancy occurred. It was especially noteworthy that in 40 cases out of the 46, or in 86.96 per cent, pregnancy occurred during the last few months of breast feeding, or when the process of weaning was taking place. Among these 46 pregnancies, also, 28 cases, or 60.87 per cent, occurred after nine months of breast feeding, and 18 cases, or 39.13 per

TABLE VI. INCIDENCE OF PREGNANCY DURING LACTATION IN 500 PREGNANCIES

LENGTH OF TIME INFANT BREAST FED (MONTHS)	NUMBER OF MONTH IN WHICH PREGNANCY OCCURRED DURING BREAST FEEDING	NUMBER OF CASES		PER CENT OF 46 CASES			
5	4th	1	}	3	6.52	}	39.13% 18 cases
6		1					
9		1					
8	5th	1	}	1	2.17		
9	6th	1	}	3	6.52		
12		1					
6		1					
8	7th	1	}	4	8.70		
9		1					
10		1					
12		1					
9	8th	5	}	7	15.22		
10		1					
12		1					
9	9th	2	}	7	15.22	}	60.87% 28 cases
10		2					
11		1					
12		2					
12	10th	5	}	5	10.87		
11	11th	1	}	5	10.87		
12		2					
13		1					
15		1					
12	12th	3	}	4	8.70		
14		1					
13	13th	2	}	5	10.87		
16		2					
18		1					
14	14th	1	}	1	2.17		
18	16th	1	}	1	2.17		
Total		46	46		100.00		

cent, occurred after from four to eight months, with very few cases in the earlier months. These figures are shown in Tables VI and VII. This information indicates that, although pregnancy occurred during lactation, it occurred at a time when the mother and baby, in most instances, did not need the protection afforded by breast feeding.

*Number of Months Between the End of Breast Feeding and Next Conception in 454 Cases in Which Pregnancy Did Not Occur During Lactation.—*

Among the 454 cases in which pregnancy did not occur during lactation, the interval between the end of breast feeding and the next conception was as follows: In 185 cases the interval was less than two months; in 246 cases, the interval was four months or less; in 102 cases, the interval was from five to nine months. This amounted to more than three-fourths of the cases, or 76.67 per cent. Of the remainder, in 51 cases, there was an interval of 10 to 14 months; and, last, in 55 cases, the interval was 15 to 39 months. These figures are shown in Table VIII.



### Borderline Cases

#### *Type I.—*

In addition to the uncertainty of the time of ovulation, fertilization and conception, there is also some uncertainty as to the duration of pregnancy and calculation of the expected date of confinement. This uncertainty as to the exact date of conception made it necessary to consider two types of borderline cases.

The first type of borderline case is divided into two categories:

1. Those cases in which the date of conception occurred such a very short time before breast feeding ended, as to make the incidence of pregnancy during lactation doubtful. This is due to the fact that, during history taking, the mother gives the number of months the baby was breast fed, but the number of months may not be complete; i.e., breast fed for nine months may mean that breast feeding was terminated at the beginning or the middle of the ninth month. Therefore, a grace period of two weeks or fifteen days is allowed in these borderline cases; that is, the date of conception may be two weeks earlier than the date breast feeding stopped in terms of complete months. Conception would then occur after breast feeding had stopped.

2. Those cases in which breast feeding stopped two weeks or less before the date of conception. Here also because of the uncertainty of details as the exact date when lactation ended in terms of complete months, a grace period of fifteen days is allowed.

Number of Month During Lactation in Which Pregnancy Occurred in Relation to Number of Cases

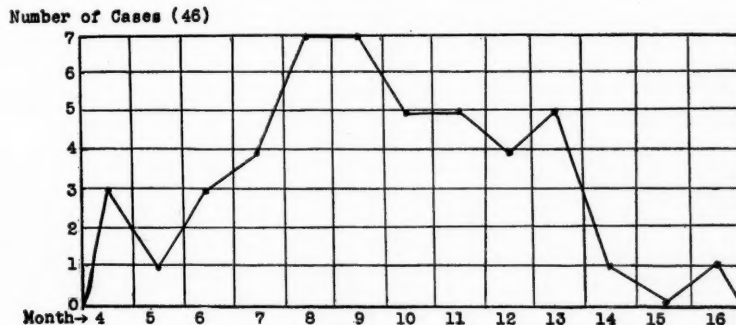


Fig. 2.

The number of cases in these two categories is explained as follows:

1. There were a total of 18 cases in which conception occurred fifteen days or less before breast feeding ended. Of these cases it was possible to check 6 with the mother in clinic. Of these 6 cases checked, 2 cases of pregnancy during lactation occurred, and these were placed among the 46 cases of incidence of pregnancy during lactation. Four patients checked did not become pregnant while breast feeding, and these were placed with the remaining 12 cases not checked among the 454 cases in which pregnancy did not occur during lactation.

2. There were a total of 30 cases where breast feeding stopped two weeks or less before conception occurred. It was possible to check 8 of these cases with the mother in clinic. In one of these 8 cases, pregnancy occurred during lactation. Of the other 7 cases checked, there was no incidence of pregnancy during lactation. The former was included among the 46 cases of pregnancy

during breast feeding. The latter 7 cases were included, with the remaining 22 cases, among the 454 cases in which pregnancy did not occur during lactation.

TABLE VII. TIME BREAST FEEDING ENDED AFTER PREGNANCY OCCURRED

	NUMBER OF MONTH PREGNANCY OCCURRED	NUMBER OF CASES	TOTAL	PER CENT OF 46 CASES	
Pregnancy occurred within the last month of breast feeding	6th	1			
	9th	2			
	11th	1			
	12th	3			
	13th	2			
	14th	1	10	21.74	
Breast feeding stopped one month after pregnancy oc- curred	4th	1			
	7th	1			
	8th	5			
	9th	2			
	11th	2	11	23.91	
Breast feeding stopped two months after pregnancy occurred	4th	1			
	7th	1			
	8th	1			
	9th	1			
	10th	5			
	11th	1			
	12th	1			
	16th	1	12	26.09	
Breast feeding stopped three months after pregnancy occurred	5th	1			
	6th	1			
	7th	1			
	9th	2			
	13th	2	7	15.22	
Breast feeding stopped four months after pregnancy occurred	8th	1			
	11th	1	2	4.35	
Breast feeding stopped five months after pregnancy occurred	4th	1			
	7th	1			
	13th	1	3	6.52	
Breast feeding stopped six months after pregnancy occurred	6th	1	1	2.17	
Total		46	46	100.00	

40 cases or  
86.96%: one  
to three  
months

6 cases or  
13.04%: four  
to six months

These figures are shown in Tables IX and X.

#### Type II.—

Lactation does not offer the same degree of protection when supplementary feedings are given, as stated earlier in this study by Rice.<sup>14</sup> This is also true during the weaning process, when other foods are substituted for breast milk. It was necessary, therefore, to consider another type of borderline case. This second type of case is also of two categories:

1. Those cases in which pregnancy occurred in the last month of breast feeding, outside of the two-week grace period, or between 16 to 31 days before breast feeding ended. In the 46 cases of incidence of pregnancy during lactation there were 10 cases, or 21.74 per cent, which occurred within the last month of breast feeding. Two of these cases occurred within the first two-

week period, and were checked in clinic as positive cases of incidence of pregnancy during lactation. Of the 8 remaining cases which occurred within 16 to 31 days of the last month of breast feeding, it was possible to confirm one case as positive. The remaining 7 cases were placed among the 46 cases of incidence of pregnancy during lactation, even though it was not possible to confirm these cases.

TABLE VIII. NUMBER OF MONTHS BETWEEN THE END OF BREAST FEEDING AND NEXT CONCEPTION, 454 CASES

NUMBER OF MONTHS	NUMBER OF CASES	TOTAL	PER CENT OF 454	TOTAL
Less than 1	67	185	14.76	40.76
1	59		13.00	
2	59		13.00	
3	38	61	8.37	13.44
4	23		5.07	
1-4		246		54.20
5	26		5.73	76.67%
6	20		4.41	
7	18		3.96	
8	23		5.07	
9	15		3.30	
5-9		102		22.47
10-14		51		11.23
15-19	21		4.62	23.33%
20-24	17		3.74	
25-29	8		1.76	
30-34	6		1.32	
35-39	3		.66	
		55		12.10-
Total	454	454	100.00	100.00

TABLE IX. BORDERLINE CASES, TYPE I (1), IN WHICH CONCEPTION OCCURRED TWO WEEKS OR LESS BEFORE BREAST FEEDING ENDED

	NO. OF CASES	PER CENT OF 18
<i>Cases Checked.</i> —		
Conception occurred while breast feeding	2	11.11
Conception did not occur while breast feeding	4	22.22
	6	33.33
<i>Cases Not Checked.</i> —		
Placed with 454 cases in which pregnancy did not occur while breast feeding	12	66.67
Total	18	100.00

TABLE X. BORDERLINE CASES, TYPE I (2), IN WHICH BREAST FEEDING ENDED TWO WEEKS OR LESS BEFORE CONCEPTION OCCURRED

	NO. OF CASES	PER CENT OF 30
<i>Cases Checked.</i> —		
Conception occurred while breast feeding	1	3.33
Conception did not occur while breast feeding	7	23.33
	8	26.66
<i>Cases Not Checked.</i> —		
Placed with 454 cases in which pregnancy did not occur while breast feeding	22	73.34
Total	30	100.00

2. Those cases in which there was an interval of less than one month between the end of breast feeding and the next conception. Of the 67 cases in which there was an interval of less than one month, 30 were accounted for in the Type I borderline case, as occurring within the first two weeks, or 15 days after breast feeding ended. Of the remaining 37 cases, breast feeding ended between 16 and 31 days before the onset of the next conception. These were placed among the 454 cases in which pregnancy did not occur during lactation, even though it was not possible to confirm them.

These figures are shown in Tables XI and XII.

TABLE XI. BORDERLINE CASES, TYPE II (1), IN WHICH PREGNANCY OCCURRED IN LAST MONTH OF BREAST FEEDING

	NO. OF CASES	PER CENT OF 10
<i>Cases Checked.</i> —		
Pregnancy occurred first two weeks	2	20.0
Pregnancy occurred last two weeks	1	10.0
<i>Cases Not Checked.</i> —	7	70.0
Pregnancy occurred last two weeks, but placed among 46 cases of incidence of pregnancy during lactation		
Total	10	100.0

TABLE XII. BORDERLINE CASES, TYPE II (2), IN WHICH THERE WAS AN INTERVAL OF LESS THAN ONE MONTH BETWEEN THE END OF BREAST FEEDING AND NEXT CONCEPTION

	NUMBER OF CASES	PER CENT OF 67
<i>Cases Checked.</i> —		
Interval less than two weeks	8	11.94
<i>Cases Not Checked.</i> —		
Interval less than two weeks	22	32.84
Interval two to four weeks	37	55.22
Total	67	100.00

### Summary

A study of the time and occurrence of pregnancy during the lactating period in 500 lactating mothers has been made to determine to what extent breast feeding protects the mother, as a natural means, in the spacing of children, to regain her health and strength, before assuming another pregnancy.

Among the 500 pregnancies studied, there were 46 cases in which a pregnancy occurred during lactation. This was 9.2 per cent of 500 pregnancies. Twenty-eight cases, or 60.87 per cent, occurred after the ninth month of breast feeding, and 18 cases, or 39.13 per cent, occurred within from four to eight months, with very few cases occurring in the earlier months. It was noted that in 40 cases out of the 46, or 86.96 per cent, pregnancy occurred during the last few months of breast feeding, or when the process of weaning usually takes place. This information indicates that although pregnancy occurred during lactation, it occurred at a time when the mother and baby, in most instances, did not need the protection afforded by breast feeding.

Among the 454 cases, or 91.8 per cent, of the 500 pregnancies studied, the interval between the end of breast feeding and the next conception was, for the most part, extremely short. In 185 cases, or 40.76 per cent, the interval was less than two months. A total of 246 cases, or 54.20 per cent, had an in-



terval of less than four months; 102 cases, or 22.47 per cent, had an interval of five to nine months. This amounted to more than three-fourths of the cases, or 76.67 per cent. The remainder, 51 cases, or 11.23 per cent, had an interval of 10 to 14 months; and 55 cases, or 12.10 per cent, had an interval of 15 to 39 months.

Two types of borderline cases were considered, because of the uncertainty as to the exact date of conception, and the uncertainty as to the exact date when lactation ended in terms of complete months. In the second type, it may be stated that there was a greater certainty in placing these cases in their respective categories because of the longer interval of time, and also because of the weaning process which is almost complete in the last two weeks of breast feeding, or where breast feeding was considered ended in terms of complete months. Thus, consideration was given to the date of conception within the first two weeks after breast feeding ended, thus allowing ample time for any discrepancy as to the exact date of conception.

### Conclusions

As a result of the figures presented in this study, the following conclusions may be made:

1. Breast feeding does protect the mother, as a natural means, in the spacing of children, to regain her health and strength, before assuming another pregnancy, as indicated in the approximately 95 per cent of cases in which pregnancy did not occur during lactation for a period of at least nine months.

2. This protection may be said to last for approximately nine months or more, if no additional supplementary or complementary formula is used.

3. In the remaining 5 per cent of cases, when supplementary or complementary feedings are used, as is the case during the weaning process in the last months of breast feeding, this protection is diminished and a greater incidence of pregnancy occurs during this period.

4. This period of nine months of breast feeding, with an additional nine months of pregnancy, would make the interval between births approximately 18 months, or less than 24 months.

5. In addition, since the procedure of breast feeding is of great benefit to mother and baby, both physiologically and psychologically, it may be said that this would be an additional aid in helping the mother to regain her full strength before assuming another pregnancy.<sup>16, 17, 18</sup>

As a result of the conclusions reached in this study, the following recommendations are suggested:

1. That the additional advantage of breast feeding as a means of ensuring natural spacing of children, to help the mother regain her health and strength before assuming another pregnancy in most cases, be included with the physiological and psychological advantages of breast feeding, in individual and group instruction of expectant parents, by doctors, nurses, maternity clinics and services, and other community agencies concerned with parent education.

2. That efforts be made to encourage breast feeding, and to help the mother continue breast feeding as long as possible. A number of studies are valuable for this purpose.<sup>1, 7, 10-11, 15, 18, 20</sup>

3. That a controlled study be conducted in a maternity service in some area where breast feeding is maintained as long as possible to secure exact figures on the incidence of pregnancy during lactation over a period of time. This area could be determined by examining certain studies.<sup>2, 4, 8</sup> A number of other factors would have to be considered in such a controlled study. Personal contact with each patient would be necessary.

4. That we should be aware of another task confronting us, even before we reach the expectant parent, and that is, the proper education of our youth and parents of the future. Fortunately, the pendulum is swinging in favor of breast feeding in many areas.

An attempt has been made in this study to demonstrate the importance of guiding, directing, and actively assisting future parents to use the best available means of safeguarding the mothers' health immediately after childbirth, by adequate natural spacing, provided by the procedure of breast feeding their babies for the length of time necessary to accomplish this objective.

I wish to acknowledge the kind assistance and guidance of Drs. Roy J. Heffernan and William A. Lynch of Brookline, Mass., in reviewing this study for its final form. The collection and interpretation of the data, and the conclusions stated are, however, my responsibility.

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## INTRALIGAMENTARY PREGNANCY\*

### The Extraperitoneal Type of Abdominal Pregnancy

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**I**NTRALIGAMENTARY pregnancy is a gestation which grows within the space made by the peritoneal folds of the broad ligament. Hence, it is an ectopic pregnancy that develops abdominally and extraperitoneally. It is essentially an abdominal pregnancy which develops retroperitoneally, and thereby presents diagnostic and therapeutic problems that differ somewhat from those associated with the more frequently seen intraperitoneal abdominal gestations. Therefore, it is regrettable that it is frequently reported just as an abdominal pregnancy without being distinguished from the intraperitoneal variety. This condition is also referred to as "broad ligament," "intraligamentous," or an "extraperitoneal" pregnancy. Champion and Tessitore<sup>1</sup> call attention to the relationship of the ovisac to the pelvic organs, which is of paramount importance. The medial boundary is the uterus, the lateral boundary the wall of the pelvis, inferiorly the pelvic floor, and superiorly the Fallopian tube. Any true intraligamentary pregnancy at term must have these boundaries. In this unusual gestation, the round ligament is frequently seen prominently on the anterior surface of the sac. We believe that this is very significant since the round ligament is frequently seen conspicuously on the anterior surface of large cystic or solid tumors of the broad ligament.

Although this form of ectopic pregnancy is the least frequent, it is nevertheless very interesting to study. Concerning the ratio of incidence of this type of extrauterine pregnancy to other ectopic pregnancies, Wilens<sup>2</sup> found it to occur once in 75; Wilson, Ekas, and Schultz<sup>3</sup> twice in 195; and Kennedy<sup>4</sup> in 1925, from several statistical sources, estimated it to occur far less frequently, namely, once in 613 ectopics. Champion and Tessitore, employing the latter ratio, computed the occurrence of intraligamentary gestation to be once in 183,900 pregnancies. Pregnancy within the broad ligament probably occurs more frequently than the estimates of Kennedy and Champion and Tessitore. It is likely to occur more often among Negroes, in whom ectopic pregnancy and chronic pelvic inflammatory disease are more frequently seen. During a period of thirteen years (1940 to 1952, inclusive) 86,622 live babies and 2,197 stillborn infants were delivered on the obstetrical service of the Cook County Hospital where over 90 per cent of the patients are of the Negro race. During this period there were 932 ectopic pregnancies, and, of these, 3 were intraligamentary and 27 were abdominal and intraperitoneal (Table I).

\*Presented at a meeting of the Chicago Gynecological Society, Feb. 19, 1954.

TABLE I. OBSTETRICAL DATA DURING THE THIRTEEN-YEAR PERIOD (1940-1952) AT THE COOK COUNTY HOSPITAL. THE FREQUENCY OF INTRALIGAMENTARY PREGNANCY\* IN RELATIONSHIP TO OTHER ECTOPIC OR INTRAUTERINE GESTATIONS IS INDICATED

Total number of live births	86,436
Total number of stillbirths	2,179
Uterine abortions unknown estimated	59,718
Total number of ectopic pregnancies	932
Intraligamentary pregnancies	3
Abdominal pregnancies	27

\*Estimated incidence once in 49,765 gestations. Ratio to all other ectopic pregnancies once in 320 gestations.

Based on Taussig's<sup>5</sup> monograph wherein the accepted ratio of abortions to pregnancies is 1 to 2.5 (in urban areas), we estimate that the possible incidence of broad-ligament pregnancies (for Cook County Hospital patients) during this period was possibly once in 49,765 gestations.

### Pathogenesis

The intraligamentary space has no direct connection with the lumen of the tube or the peritoneal cavity; therefore, the fertilized ovum cannot enter this space directly to implant primarily therein. An intraligamentary pregnancy must first implant elsewhere and, therefore, only secondarily develops into the broad-ligament space, the only possible exception being the extremely rare and questionable primary abdominal pregnancy. Three conditions must be fulfilled to permit an ovisac to develop secondarily into the broad ligament. First, when the primary implantation is in the tube, it must attach itself along the line of attachment of the mesosalpinx. Second, if rupture of the tube occurs, it must take place very early in the life of the embryo, otherwise the trophoblast cannot secure a secondary nidation. This trophoblastic invasive action is lost early because the embryo soon develops well-formed villi that are less concerned with invasiveness. Third, the interval between primary and secondary implantation must be of short duration or death of the fetus will occur.

Roxas and Villarama<sup>6</sup> do not believe that a secondary implantation is possible after an abrupt separation of the ovisac. In their case they cite a primary implantation of the ovum upon the posterior peritoneal surface of the broad ligament that eventually entered the intraligamentary space, the blastodermic vesicle burrowing through the peritoneum into this space of loose areolar tissue which is conducive to further growth and development. A secondary broad-ligament transplantation must be a gradual one if the embryo is to continue its development into the advanced fetal form. There is, therefore, no abrupt transition of the ovum into the folds of the broad ligament. If this occurs, however, the ovum dies, and the bleeding that follows results in a hematoma that distends the broad ligament. Two such cases have been described by Wilens. Intraligamentary pregnancies are therefore preceded by an ectopic gestation that secondarily extends into the broad-ligament space. The primary anatomic sites for implantation prior to invasion into the broad-ligament space are: (1) intrauterine portion of the tube (interstitial preg-



nancy), (2) extrauterine portion of the tube (tubal pregnancy), (3) ovarian pregnancy, and (4) primary abdominal pregnancy.

Ash<sup>7</sup> and Wynne<sup>8</sup> have stated that interstitial pregnancies may under rare circumstances grow into the broad ligament. This was recently confirmed by the senior author,<sup>9</sup> who removed an unruptured two months' gestational sac that was definitely growing into the broad ligament. To remove this ectopic gestation, it was necessary to incise the broad ligament between the round ligament and the tube and to excise the left cornual portion of the uterus. Itzkin,<sup>10</sup> in 1934, reported an early ovarian pregnancy that was growing into the broad ligament. This is quite similar to the mechanism whereby cysts of the ovary develop into broad-ligament cysts. In this phenomenon, there is no rupture with secondary implantation of the pregnancy but a continued, gradual growth of the ovisac into the mesovarium and the folds of the broad ligament. Novak<sup>11</sup> believes that intraligamentary pregnancy can develop from a primary tubal implantation when rupture takes place at some point along the line of attachment of the mesosalpinx. He states, however, that "the placental growth then proceeds more and more into the intraligamentary space, as described in connection with secondary abdominal pregnancy." Wolfe and Neigus<sup>12</sup> recently reported 3 cases of early intraligamentary pregnancy and contend that they were all primarily implanted in the Fallopian tube.

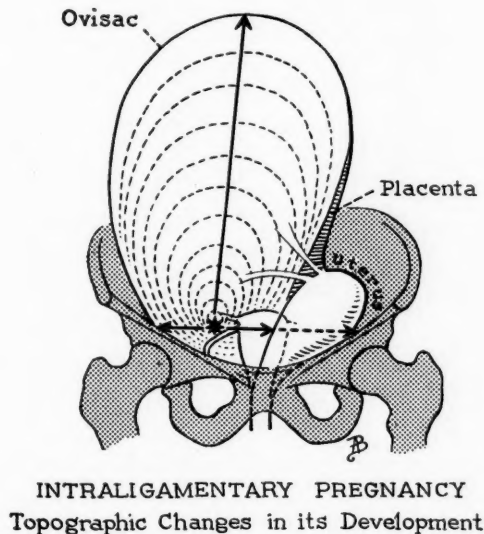


Fig. 1.—This diagrammatic sketch is based upon the reconstructed picture of Case 2. The asterisk indicates the initial site of intraligamentary implantation. The arrows show the direction of fetal expansion and anatomic positional alterations that this imposes upon the vagina, uterus, and broad-ligament structures.

### The Clinical Picture

The diagnosis is hardly ever made prior to laparotomy or postmortem visualization of the pelvic organs. In general, the symptoms, clinical picture, and pelvic findings in the earlier months of gestation and onward are inconstant and noncharacteristic. The syndrome resembles the course of an advancing

abdominal pregnancy. While a few women may be fairly comfortable in the earlier months, a nagging discomfort ultimately predominates. The growth of the fetus in the broad ligament evokes certain changes which may explain much of the symptomatology that was not understood preoperatively. The growing ovisac progressively distends the broad ligament, putting its peritoneal investment under increasing tension. Peritoneal tissues, when thus disturbed, are well known to evoke pain, the latter undergoing temporary remissions during bed rest or hospitalization. In a review of numerous case reports, it was noted that despite the hospitalization of many patients one or more times prior to the final admission the diagnosis was still undetermined. The rapidly distending peritoneal covering of the broad ligament results in its thinning, giving rise to small surface abrasions. This particularly involves the superior surface over the ovisac in the latter months of gestation because of pressure distention by the growing fetus. Therefore, adhesions of bowel and omentum are particularly noted at this site in the advanced pregnancies. The fetal sac probably was perforated in 2 of our cases just prior to surgical intervention, giving rise to a picture simulating ileus.

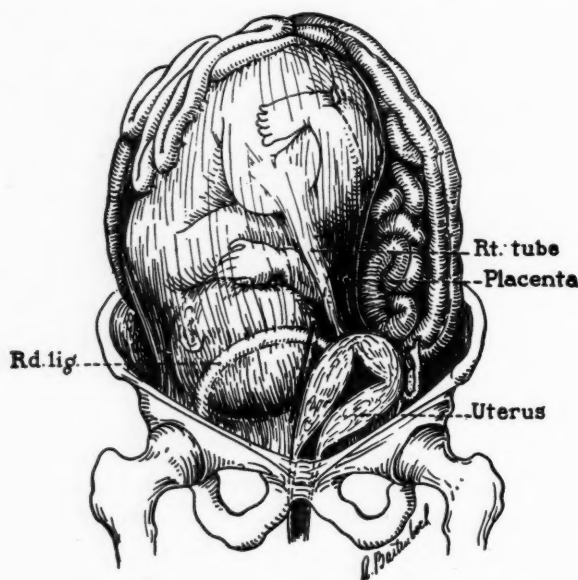


Fig. 2.—Reconstruction of intraligamentary term pregnancy of Case 2. Sketch made immediately after the operation. The line bisecting the right round ligament was the course of the incision that opened the fetal sac. Numerous loops of bowel and omentum were adherent to the peritoneum at a higher level. The vaginal portion of the cervix appears to be drawn up into the uterus.

The distended broad ligament displaces the uterus laterally or obliquely to one side. We have noted (as others have) the cervix to be pulled up high into the vagina and likewise displaced to one side (Figs. 1 and 2). This phenomenon is not limited to pregnancies in the broad ligament. It occurs also in some of the intraperitoneal abdominal pregnancies. Inevitably, at the time of laparotomy, the surgeon notes a more or less characteristic picture, and by its proper interpretation may frequently for the first time suspect the type of advanced ectopic pregnancy with which he is dealing. The surgeon making the usual

suprapubic midline incision finds the uterus pushed to one side, and at first it is out of his view. The lowermost fetal pole is noted covered with anterior broad-ligament peritoneum, and the round ligament is often prominently in the surgical field. This area, the least vascular and minimally involved by adhesions, is the most suitable for incising and extracting the fetus. The round ligament was incised in 2 of our cases in order to facilitate extraction of the fetus. With the fetus removed, and the umbilical cord divided, the uterus now became visible. One thereby noted that the ovisac occupied an area wherein the uterus was medial, and the pelvic and abdominal walls were lateral. The treatment of the pelvic organs and the placenta depends upon the circumstances present, and the judgment of the surgeon. Unlike the placenta in an abdominal pregnancy, the placenta in intraligamentary gestation develops retroperitoneally and need not be subjected to a hard and fast rule that it should not be disturbed. The placenta very frequently is high and may be found isolated and attached to the redundant and easily removable remnant of the broad ligament. If the placenta is not in the vicinity of the bowel attachments or does not extend too deeply toward the base of the broad ligament with the redundant peritoneal tissue, it may be removed. Some have found that by removing the uterus hemostasis is more easily attained, especially if the placenta is attached to its broad-ligament surface. If the fetus has been dead sufficiently long the vascular attachments become obliterated, and the removal of the placenta is safe. If there is doubt, however, it is better to leave it in situ undisturbed. Blood replacement and antibiotic therapy are features in the management that make recovery more likely.

We herewith present three additional cases of term intraligamentary pregnancy.

CASE 1.—Mrs. M. H., a 35-year-old Negro woman, para 0, gravida ii, last menstruated May 15, 1943. In 1942 she had had a left salpingectomy, right salpingostomy, appendectomy, and uterine suspension. This patient was first seen on July 20, 1943, when she had a sudden attack of faintness, dizziness, and dull pain in the right lower abdomen followed by slight vaginal bleeding. She was admitted to Cook County Hospital where a pregnancy test was found to be positive, and was discharged from the hospital on August 14, with a diagnosis of threatened abortion. Six weeks later, on September 28, she was readmitted to the hospital. Abdominal examination revealed a movable mass in the right lower abdomen extending 4 cm. above Poupart's ligament. This mass was not tender. On vaginal examination the cervix was found to be high and compressed against the symphysis pubis and firm. The right and posterior fornices were depressed by a boggy mass. The left fornix was high with the uterus against the left lateral pelvic wall. The impression was that of intrauterine pregnancy and a right ovarian cyst or pyosalpinx. The patient was treated expectantly and discharged in a few days to be followed at the prenatal clinic. On November 19, a diagnosis was made of an intra-abdominal pregnancy. On December 10, x-ray showed the fetal skeleton. Fetal heart tones were heard in the right lower quadrant. On March 17, laparotomy was performed. A cystlike mass was seen occupying the lower abdomen, and extending to about 4 cm. above the umbilicus. The cyst wall was thin, and the fetus was plainly visible. A longitudinal incision was made in the anterior wall of the cyst and the infant delivered. After delivery, it was noted that the uterus was in the left lower abdomen, and anterior to the cyst wall. The placenta was attached to a round structure whose external surface was glistening like peritoneum, which tapered to the right uterine cornu. It was thus noted that the products of conception were entirely retroperitoneal. The cystlike

structure was incised circularly and removed. The bottom of the cyst cavity was packed with gauze and the abdomen was closed in layers, except for the exit of the drain which was gradually removed after the sixth day.

The infant was a normal female, weighing 5 pounds, 7 ounces, and cried immediately after delivery. The mother and child left the hospital in good condition on the fourteenth hospital day. Pathological examination identified the Fallopian tube and placenta in the dome of the cystlike structure.

CASE 2.—J. W., a 35-year-old Negro woman, para ii, gravida iii, was admitted to the obstetrical service of the Cook County Hospital on June 30, 1947, because of pain in the right lower quadrant for the past five months. Her last normal menstrual period was on January 17. She described the pain as a dull ache which was constantly present in the right lower quadrant, and which was aggravated by moving about. At this time she was considered to have a six-month intrauterine pregnancy with a fibroid in the right broad ligament. The symptoms subsided after five days, and she was discharged to the prenatal clinic.

She felt fairly well for one month, after which she developed ankle edema and epigastric pains for which she was readmitted on Aug. 29, 1947. Her blood pressure was normal, and she had gained 28 pounds in approximately 32 weeks of gestation. After 13 days all symptoms subsided on bed rest and she again was discharged with the assumption that the fibroid uterus was the cause of the edema. She was followed in the prenatal clinic. Examination on her last visit to the clinic on Sept. 30, 1947, revealed nothing unusual, and the fetal heart tones were normal. On October 3, however, it was necessary to readmit her to the hospital. At this time she complained of constant severe pain in the left lower quadrant. The abdomen was markedly distended and tense. She vomited repeatedly. Fetal heart tones now could not be heard. The treatment consisted of Levine suction, blood, and penicillin. Vaginal examination revealed that the cervix was drawn up high into the vault on the left side. The cervical opening and the lips were flush with the top of the vagina. Above, on the left side a hard mass was present which was regarded as a fibroid or possibly the uterus. Another hard mass, the size of the fetal head, occupied the right lower quadrant. Although an abdominal pregnancy was considered, the impression was that the patient's condition was the result of an intrauterine pregnancy with the degenerating fibroids that were obstructing the pelvic passages. On October 6, with the patient somewhat improved, the abdomen was opened through a low midline incision. There was a plastic chemical peritonitis with meconium-stained fluid and multiple adhesions of the fetal sac to the parietal peritoneum and bowels. Anatomical landmarks were difficult to make out. A large edematous round ligament coursed prominently obliquely upward across the surgical field (Fig. 2).

The fetal head was felt medially and inferiorly to this ligament. To extract the fetus, a longitudinal incision was made over the region of the head, and a macerated fetus was extracted. With the fetus removed, the placenta was readily felt inside the sac, and separation was effected easily with minimum bleeding. It now was noted that there had been an old rupture on the superior surface aspect of the sac which had been closed over by dense adhesions containing bowel. The portion of the large redundant fetal sac free of bowel attachment was removed. The mass occupying the left lower quadrant proved to be the uterus, and the other mass in the right lower quadrant felt on vaginal examination was the fetal head. When the uterus was brought into the operative field it was noted that the right broad ligament had been severed down to the uterine vessels. A supracervical hysterectomy was then performed. The abdomen was then closed in the usual manner. The patient made an uneventful recovery and was discharged on the fourteenth postoperative day.

The tissue available for examination by the pathologist was a supracervically amputated uterus which measured 9 by 9 by 5 cm. On the right side of the fundal portion of



the uterus on its broad-ligament surface there was evidence of placental attachment. The tube that was in the removed redundant portion of the fetal sac was found to be patent. The placenta contained several white infarcts.

CASE 3.—Mrs. M. D., para 0, gravida i, 35-year-old Negro woman whose last menstrual period was on April 6, 1950, and whose expected date of confinement was Jan. 13, 1951, was admitted to Cook County Hospital in June because of vomiting, and severe abdominal pain. On examination the diagnosis was intrauterine pregnancy with pelvic inflammatory disease and hyperemesis. She was treated conservatively and, because of anemia, 750 c.c. of blood was given. She was discharged in a week as improved. She was readmitted on Oct. 1, 1940, complaining of periumbilical pain. This was treated with sedation and she was discharged after one week in the hospital, improved. A third admission was on Nov. 13, 1950; this time she entered complaining of severe abdominal pain, left upper quadrant pain, faintness, nausea and vomiting. Examination showed a distended abdomen, exquisitely tender. Vaginal examination revealed the fetal head to be in the pelvis with the cervix drawn up high to the right. As the x-rays were inconclusive, the uterus was sounded and the probe went in for a distance of  $3\frac{1}{2}$  inches. Lipiodol was injected into the uterine cavity and the x-rays revealed the fetal body to be outside the uterine cavity (Fig. 3).



Fig. 3.—Relationship of fetus to uterus portrayed by Lipiodol injection (the cervix is pulled up high to the right).

On Nov. 22, 1940, she was operated upon under local and general anesthesia. An intraligamentary pregnancy was found, and the baby was extracted through an incision into the less vascular left broad ligament. The left round ligament was prominent in the surgical field, and was included in this incision. The umbilical cord was ligated close to the placenta (the latter was not disturbed). The left round ligament was sutured back to its original attachment to the uterus and the broad ligament was closed. The patient was given two whole blood transfusions, one before and the other during operation, each

transfusion consisting of 2 pints. There was no severe blood loss and the transfusions were administered because of severe secondary anemia. The baby, who weighed 3 pounds, 8 ounces, at birth, died fourteen days later and the findings at autopsy were prematurity and atelectasis. The patient made an uneventful recovery and was discharged on the twenty-first postoperative day.

### Summary and Conclusions

Intraligamentary pregnancy is the rarest of extrauterine gestations. The ovisac develops extraperitoneally within the leaves of the broad ligament. This ectopic pregnancy does not primarily implant in the broad ligament. The original sources of this extrauterine pregnancy are tubal pregnancy, cornual or interstitial pregnancy, ovarian pregnancy developing into the mesovarium, or a primary abdominal pregnancy implanted on the posterior surface of the broad ligament. From these original sources, the ectopic gestation develops secondarily into the intraligamentary space. If a tubal pregnancy suddenly ruptures into the broad ligament, embryonic or fetal life frequently ceases, and a broad ligament hematoma results. An intraligamentary pregnancy may continue to the advanced stages of gestation, and is frequently undiagnosed until the abdominal contents are visualized at laparotomy. In advanced gestations, it is comparable to a large-sized intraligamentary cyst. The uterus is considerably displaced to one side, and the round ligament is prominently visible on the lower aspect of the gestational sac.

The placenta develops retroperitoneally within the ovisac. If the after-birth is within the redundant and easily removable remnants of the broad ligament, and is not close to bowel attachments, or does not extend toward the base of the broad ligament, it can be removed. Removal of the uterus will facilitate hemostasis if the placenta is attached to it. Three additional cases of advanced intraligamentary gestations were herewith included. One baby lived, another succumbed in fourteen days, and a third was stillborn.

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### Discussion

DR. THOMAS W. McELIN.—In 1951, I discussed a case of term, intratubal pregnancy without rupture with Dr. L. M. Randall. The literature was reviewed in detail and we suggested diagnostic criteria for the precise recognition of this entity. In view of this experience, it seems to me that the most logical contribution I can make to this

evening's program is to emphasize where, in our total knowledge of term ectopic gestation, the interesting and informative data presented by Dr. Kobak and his associates are to be properly catalogued.

Ectopic pregnancy, by definition, includes all instances of pregnancy outside of the uterine cavity. The incidence of this complication has been estimated by Schumann at 1 in 300 pregnancies. Mall has further postulated that only about 1 per cent of ectopic gestations go to full term but clinical experience suggests that even this small figure is exaggerated. Intraligamentous term pregnancy, therefore—just one of the variants of term ectopic gestation—with a fully developed fetus is an obstetrical rarity. The authors have been most fortunate to be able to study so sizable a group of cases.

A total listing of all the possible extrauterine positions where nidation and development might occur would include the following: abdominal (primary, secondary), ovarian (primary, secondary), ovarioabdominal, tuboovarian, tuboabdominal, intratubal (ampullary, isthmic, interstitial), intraligamentary, tubouterine, pregnancy in a closed rudimentary or accessory horn, pregnancy occurring after subtotal hysterectomy (in the cervical stump, in a Fallopian tube) and cervical.

The four varieties of term ectopic gestation most commonly discussed in the literature and in textbooks are: (1) *abdominal* pregnancy of which some 280 plus cases have been reported, (2) *ovarian* pregnancy of which some 100 cases have been documented but only a lesser number (approximately 60) have been authenticated, (3) term *intratubal* pregnancy concerning which several publications have recently appeared, and (4) the authors now redirect our attention to the *intraligamentary* variety.

The diagnosis of abdominal pregnancy is rarely questioned. It is the still more unusual types of term ectopic gestation, such as ovarian, intratubal, or intraligamentous pregnancy of which the legitimacy is challenged when the breathless proponent tells of his "interesting case." The authors reflect on the haziness of this situation when they comment that cases such as theirs are often reported "just as an abdominal pregnancy." In an endeavor properly to separate these variants, attempts have been made to establish diagnostic yardsticks by which a given case might be measured. Hence, the criteria of Spiegelberg for the ovarian variety of extrauterine pregnancy have been accepted and, as mentioned, we have recently submitted criteria for the proper identification of term intratubal pregnancy. We suggested: (1) that complete extirpation of the fetal sac and products of conception be achieved by salpingectomy; (2) that there be no gross or microscopic evidence of tubal rupture; (3) that ciliated columnar epithelium be demonstrated at some few points in the inner lining of the sac, and (4) that smooth muscle be found in the sac wall at multiple sites and at considerable distances from normal, undilated tube. In 1951, 45 cases of term intratubal pregnancy were available for review in the literature and we calculated a fetal mortality of approximately 75 per cent and a maternal mortality in the neighborhood of 10 per cent.

Now, the authors remind us of the anatomical criteria for identification of an intraligamentary pregnancy as enunciated by Champion and Tessitore. In addition, Dr. Kobak emphasizes that the round ligament is frequently seen on the anterior surface of the sac. Other identifying data tabulated by Wolfe and Neigus included the observations that there is usually upward and lateral displacement of the uterus, relative fixation of the gestational sac, depression or obliteration of the affected vaginal fornix, and the placenta is usually superiorly located in relation to the fetus.

In terms of establishing an incontrovertible criterion for the identification of an intraligamentous pregnancy, I propose that by microscopy no recent disruption of the inferior wall of the Fallopian tube be demonstrable other than understandable trophoblastic invasion. In this manner, we would have microscopic criteria to separate the true variants of term ovarian, term intratubal, and term intraligamentous pregnancies from the larger group of term abdominal pregnancies. A careful description of the anatomy encountered at either surgery or necropsy in these unusual cases would also assist in more selective division of term extrauterine pregnancy into its several anatomical sites.

Other symptoms and signs relating to advanced and late extrauterine pregnancies which we feel are important enough to list and emphasize are the following: primigravidas are more frequently affected; a history of infertility is often noted; a higher incidence is observed in the Negro race; an "uncomfortable pregnancy" with "nagging" abdominal distress is often described; indigestion, constipation, irregular bleeding, and disproportionate anemia are reported; histories of false labor and unsuccessful attempts at induction are commonly given; the absence of Braxton Hicks contractions when the uterus is palpated near term, abnormal presentations of the fetus with unusual ease of palpation; absence of change in fetal position from one examination to the next and the presence of a firm, long cervix and a small, empty uterus may be important diagnostic clues.

Hysterograms are of great help and should be more widely used in cases of suspected advanced ectopic gestation in which there is no infection and, particularly, if fetal death has occurred. Microscopic examination of the fetal sac should be more widely performed.

In addition to the preceding commentary, I wish to direct two questions to the authors:

1. I am curious as to whether any significant ureteral problems were encountered in their cases or any that they surveyed in the literature. This structure must always be in frightening proximity to the inferior boundary of the intraligamentous ovisac.

2. I cannot resist an inquiry regarding the time selected for abdominal delivery in Case 1, the case wherein true fetal survival occurred. Laparotomy was performed approximately three weeks after the expected date of confinement. Was this date selected because of pain, bleeding, or was the diagnosis of an extrauterine gestation ultimately made? One cannot help but speculate how long an extrauterine pregnancy might proceed with a living fetus. The issues of intrauterine pressure and rupture of the membranes having been eliminated, the limiting factors to the successful continuation of an extrauterine pregnancy would seem to be the extent of trophoblastic invasion of adjacent organs and/or placental senescence. Conceivably, might not an extrauterine pregnancy be maintained for a significant time beyond accepted intrauterine limits? A baby might even be carried through the period of colic!

I appreciate the opportunity of discussing this paper and desire to commend the authors on their presentation.

DR. KOBAK (Closing).—I would like to answer the questions raised by Dr. McElin. In perusing the literature and in the cases I have encountered, we have not had any ureteral problems. We have never seen the ureters. They have been displaced from the field of operation.

Concerning the question about the expected due date of Case 1, this case was operated on by the late Dr. Rudolph. He made extensive notes but never published the case. When he died his family turned over his notes to us. I tried to locate the history to verify the date given by Dr. Rudolph in his notes. I was aware of the fact that this baby was apparently delivered long after the expected date of confinement.\* I tried to get hold of the original history to see if there had been an error, but the record was not available. Concerning any type of abdominal pregnancy, we have noted that the babies are usually smaller. These fetuses can die at any time. Therefore, whenever there is a prospect of getting a live baby, surgical means should be used to do this without delay. Recently I had occasion to examine a patient who had an abdominal pregnancy and found the baby quite small. It was past the due date and when we opened the abdomen we found the baby weighed only 3 pounds, 2 ounces. I agree with Dr. McElin that it is better to remove these babies surgically when you have the best chance for their survival because anything unfavorable can happen.

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\*Shortly after the presentation of this paper we were informed that Dr. Rudolph had scheduled his patient for an abdominal delivery (five weeks earlier) but she refused to permit this.



## THE INFLUENCE OF ANTIBIOTICS ON PREGNANCY TESTS IN RATS AND RABBITS

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SINCE the introduction of antibiotics and antibiotic supplements in some laboratory animal stock diets, evidence has accumulated that rats and rabbits raised on such rations when used for the pregnancy test may give a higher percentage of false reactions than those animals maintained on ordinary stock diets. This investigation was undertaken to determine whether rats and rabbits raised on diets containing added antibiotics or antibiotic supplements would give results comparable to those obtained on animals raised on similar rations without added antibiotics. Although a considerable number of comparisons were made with rabbits (Friedman test), particular emphasis has been placed on rats in this study.

### Materials and Methods

*Rat Test.*—Immature female albino rats, Sherman strain, 24 to 30 days of age, of 40 to 60 grams' weight, were used. They were from colonies maintained on the following dietary regimes:

1. A colony fed a well-known commercial pelleted diet containing no added antibiotic and tested periodically to ensure absence of antibiotic activity (*Diet A*).
2. A group of rats maintained on a commercial rat diet containing antibiotic supplements. The immature female rats used from this colony were the offspring of rats fed on this diet for three to eight months (*Diet B*).
3. A colony of rats fed Diet A in mash form supplemented with 0.6 per cent Aureomycin-B<sub>12</sub> T.F.5\* residue. Test rats used from this group were from mothers on the diet one to two months (*Diet C*).

*Rabbit Test.*—For the Friedman test young adult female rabbits were kept in separate cages at all times and fed separately. The rabbits were divided in two diet groups:

1. *Group A*: These animals were fed Diet D, a pelleted commercial ration containing added antibiotic residue.
2. *Group B*: These rabbits were fed Diet E, an antibiotic-free commercial rabbit ration.

The interval of time between collection and injection of the urine varies from 2 to 6 hours and 24 to 30 hours as shown in Table I, and summarized in Table II.

The rats were injected with 2 ml. urine intraperitoneally in the right and left abdominal quadrants.

Since the gonadotropic hormone deteriorates at room temperature, the urine specimens were refrigerated at all times prior to injection. The rats were sacrificed 22 to 24 hours after injection and the ovaries exposed for examination.

\*Aureomycin-B<sub>12</sub> Therapeutic Formula 5 is a product of Lederle Laboratories, Pearl River, N. Y., containing per pound 5 Gm. Aureomycin and 0.5 mg. vitamin B<sub>12</sub>.

TABLE I. INFLUENCE OF ANTIBIOTICS ON PREGNANCY

SAMPLE	CONTROLLED GONADO- TROPIC HORMONE	RATS				RABBITS	
		AGE OF URINE SAMPLE AT TIME OF INJECTION (HOURS)					
		2-6 DIET A	24-30 DIET A	24-30 DIET B	24-30 DIET C	24-30 DIET D	24-30 DIET E
1	N	N N	N N	N N			
2(1)	P	P P	P P	P P			
3	P	P P	P P	P P			
4	P	P P	P P		P n	P	P
5(1)	P	P P	P P		P P		
6	P	P P	P P		P P	P	P
7	P	P P	Pfn		P P		
8	P	P P	P P		P P	P	P
9	P	P P	P P		P P		
10	P	P P	P P		P P		
11	P	P P	Pfn		P n		
			Pfn		P P		
12(1)	P	Pfn			P P		
13	N	N N			N N		
14	N	fp N			fp N	N	N
15	P	Pfn	Pfn		P P		
16(1)	P	Pfn			P P		
17	P	P P			P P	P	P(4)
18	P	P P			P P		
19(2)	N	fp N	fp N		N N		
20	P	P P	P P		P P		
21(3)	N	N N	N N		N N		
22(3)	P	P P	P n		P P		
23	P	P P	P P	P P			
24	P	P P	Pfn	P P		P	
25	P	P P	P P	P P			
			P P	P P			
26	P	P P	P P	P P			
			P				
27	P	P P	Pfn	P P			
28	N	N N	N N	N N			
29	N	N N	N N	N N			N
30	P	P P	P P	Pfn	P P	P	P
31	N	N N	N N				
32	N	N N	N N	N N			
33	N	N N	N N	N N			
34	N	N N	N N	N N			
35	N	N N	N N	N N	N N		
				Nfp			
36	N	N N	N N	fp N			
				fp N			
37	N	N N	N N	N N			
		Pfn	fp N				
38	P	Pfn	Pfn	Pfn			
39	N	fp N	N N	N N			
40	N	N N	N N	N N			
41	N	N N	N N	N N	N N	N	
42	N	N N	N N		fp N	N	
43	N	N N	N N	fp N			
44	N	N N	N N	N N			
45	P	P P	P P	Pfn			
				fnfn			
46	P	P P	P P		P P		
47	P	P P	P P		P P		
48	P	P P	P P		P n		
49	N	N N	N N		N N		
50	P	P P	P P		P n		
51	N	N N				N	
52	P	P P				P	
53	P	P P				P	

TABLE I. CONT'D

SAMPLE	CONTROLLED GONADO- TROPIC HORMONE	RATS				RABBITS	
		AGE OF URINE SAMPLE AT TIME OF INJECTION (HOURS)					
		2-6 DIET A	24-30 DIET A	24-30 DIET B	24-30 DIET C	24-30 DIET D	24-30 DIET E
54	N	fp N	N N			N	
55	P	P P				P	
56	P	P P				P	
57	P	P P				P	
58	N	N N				N	N
59	P	P P				P	P
60	P	P P				P(4)	
Total of tests		120	97	58	58	19	9

*Explanation:*

- P, Controlled positive result for chorionic gonadotropic hormone.  
 N, Controlled negative result for chorionic gonadotropic hormone.  
 fp, False positive result.  
 fn, False negative result.  
 Diet A, Commercial antibiotic-free rat ration.  
 Diet B, Commercial pelleted diet containing added antibiotic residue.  
 Diet C, Diet A in mash form with 0.6 per cent Aureomycin-B<sub>12</sub> T.F.5.  
 Diet D, Commercial antibiotic-free rabbit ration.  
 Diet E, Commercial rabbit ration containing added antibiotic residue.  
 (1) Patients with suspected chorionepithelioma.  
 (2) Patients with recent abortion.  
 (3) Patients—one with suspected and one with a known case of hydatidiform mole.  
 (4) Injected intraperitoneally.

TABLE II. INFLUENCE OF ANTIBIOTICS ON PREGNANCY TESTS

	CONTROLLED GONADO- TROPIC HORMONE	RATS				RABBITS	
		AGE OF URINE SAMPLE AT TIME OF INJECTION (HOURS)					
		2-6 DIET A	24-30 DIET A	24-30 DIET B	24-30 DIET C	24-30 DIET D	24-30 DIET E
Total of tests		120	97	58	58	19	9
Positive	36	40-32	29-20	15-10	23-17	13	6
Negative	24	20-28	20-28	14-19	6-12	6	3
False posi- tive		3-0	2-0	3-1	2-0	0	0
False nega- tive		0-4	1-7	1-4	0-4	0	0
Total false reactions		7		9	6	0	0
Per cent false re- actions		5.8		15.5	10.4	0	0

The test was considered negative if the ovaries were pale, creamy in color, or slightly pinkish, with the surface showing only minute colorless follicles; and positive if one or both of the ovaries were enlarged, reddened with very distinct red follicles, corpora hemorrhagica, and blood vessels injected. Due to the fact that some rats (3.5 per cent) are refractory, each test was performed on two rats derived from the same diet group. In the Friedman test, 10 ml. of urine, 22 hours after collection, was injected into the marginal ear vein of virgin rabbits which had been housed individually. The two rabbits labeled "4" in Table I were injected intraperitoneally because the veins were sclerosed. The reactions in these two rabbits were as satisfactory and clear as in the rabbits injected intravenously.

The tests read 46 to 48 hours after injection were considered positive when the ovaries showed hemorrhagic follicles and the uterus was enlarged, hyperemic, with injected blood vessels.

### Results and Comment

In selecting urine samples for this study an attempt was made to obtain urine specimens from women: (1) whose specimens gave an equivocal reaction; (2) with chorionepithelioma, (3) with suspected hydatidiform mole, and (4) who had aborted. Selecting samples under these conditions lowered the accuracy of our tests 13.3 per cent. This figure includes 3.5 per cent of refractory rats.

The reactions in the ovaries of rats fed with antibiotic-free diet or antibiotic-residue-containing diet showed no practical difference, but the rats fed with diet containing Aureomycin T.F.5 in mash form, gave superior results because the rats were more sensitive in detecting the chorionic gonadotropic hormone.

The percentage of false results was higher in rats injected with urine specimens 24 to 36 hours old than with urine 2 to 6 hours old. This was probably due to the partial destruction of the hormone during the period when the specimens were removed from the refrigerator and allowed to reach room temperature. It is evident in Table I that rats fed "B," a commercially prepared antibiotic-residue-containing diet, were less sensitive in detecting the chorionic gonadotropic hormones present in the urine than those fed Diet A or C. Thus the percentage of refractory rats from Diet B reached 15.5 per cent compared to 10.3 per cent and 10.4 per cent for A and C respectively.

Obviously there is a higher percentage of false results with rats fed commercial pelleted diet containing antibiotic residue than rats fed antibiotic-free diet. Although the results in rabbits from the two diet groups were equal the rabbits receiving antibiotics did give positive tests which were more striking than positive reactions in the controls.

### Summary

Pregnancy tests were made on urine specimens from women by injection of the specimens into rats and rabbits kept on diets with and without antibiotics.

1. One hundred twenty rats on antibiotic-free diet injected intraperitoneally with 2 c.c. of urine collected 2 to 6 hours previously, gave 5.8 per cent false results.

2. Twenty-seven rats on antibiotic-free ration injected intraperitoneally with 2 c.c. of urine, 24 to 30 hours after collection, gave 10.3 per cent false results.

3. Fifty-eight rats obtained from a colony kept 3 to 6 months on commercial diet with antibiotic gave 15.5 per cent of false results when injected with 2 c.c. of urine 24 to 30 hours after collection.

4. Fifty-eight rats from a colony kept on 0.6% Aureomycin T.F.5 for 20 to 60 days gave 10.4 per cent of false results when injected with 2 c.c. of urine 24 to 30 hours after collection.

5. Nineteen rabbits maintained on a diet with antibiotics from 1 to 4 months gave no false results when injected intravenously with 10 c.c. of urine. No false reactions were obtained in rabbits kept on the control diet. The positive tests were more striking in the rabbits fed antibiotics.



## Department of Case Reports New Instruments, Etc.

### A METHOD OF MUCOFASCIAL APPROXIMATION IN ANTERIOR COLPORRHAPHIES

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**A**PPROXIMATION of the mucosa to the pubovesicocervical fascia is desirable in any anterior vaginal wall repair to eliminate dead space, control bleeding, and provide a better anatomical result. This is usually accomplished by dipping down with the needle and picking up a bite of fascia as the closure of the mucosa is completed. This has several disadvantages in that the fascia may be difficult to pick up if it has been approximated snugly under the bladder, it may be weakened by additional bites of the needle, a fascial suture may be cut by the needle and the depth of the bite may be uncertain.

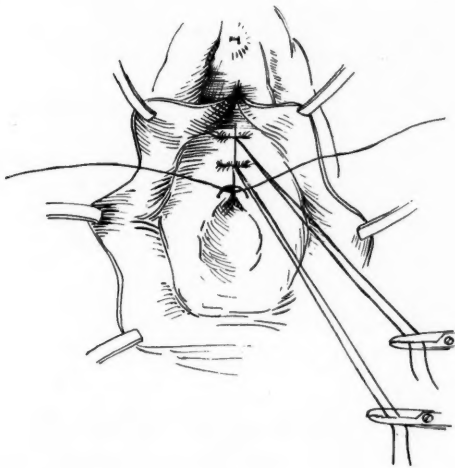


Fig. 1.

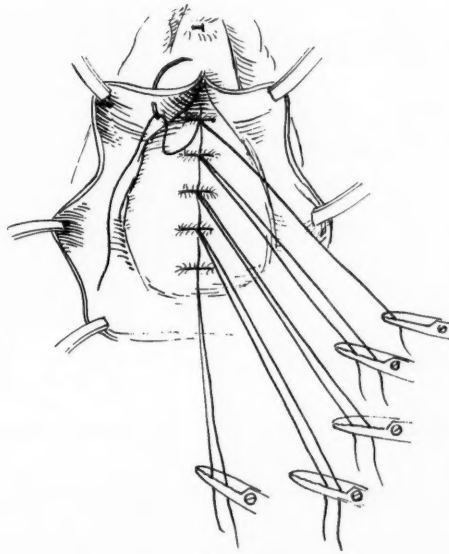


Fig. 2.

Fig. 1.—The pubovesicocervical fascia is united in the midline. The sutures are clamped and left long.

Fig. 2.—The excess anterior vaginal wall has been trimmed. One end of the top fascial suture has been threaded on a needle and is being passed through the mucosa from within out. The other end of the suture is then threaded and the needle passed through the opposite edge in the same manner.

In order to overcome these disadvantages, I have used a simple modification of the usual technique as shown in Figs. 1, 2, and 3. After the bladder and urethra have been well freed and the cystourethrocele reduced by midline approximation of the pubovesicocervical fascia with interrupted No. 0 chromic catgut, these sutures are clamped and left long. The excess anterior vaginal wall is then trimmed and both ends of the long fascial sutures are threaded on a needle and passed through the mucosa from within out. After the sutures are tied, the mucosa is held firmly against the fascia. Inversion of the edges may be prevented by everting them with tissue forceps as they are tied. Additional superficial midline and lateral sutures may be taken as necessary for approximation.

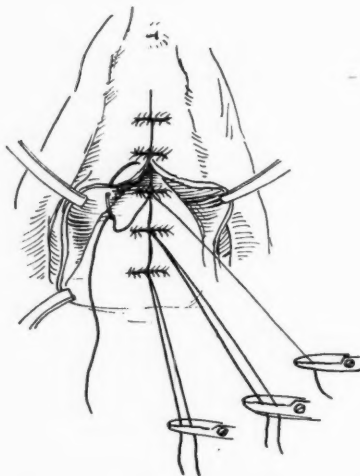


Fig. 3.—The third suture is being taken. The two upper ends have been tied, securing the mucosa firmly against the fascia. The lower two sutures will complete the approximation.

This technique may be used with equal advantage in the Manchester operation or in anterior repair combined with vaginal hysterectomy.

## SEVERE LACERATIONS OF THE UTERUS FOLLOWING A CRIMINAL ABORTION\*

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ON JUNE 5, 1953, at 9:30 P.M. a young woman was brought into the Henrotin Hospital emergency room in a wheel chair. She was accompanied by a doctor who gave the following information:

The patient was first seen by him at 2:30 P.M. on June 4, thirty hours prior to admission to our hospital. During her stay at his office, about thirty hours, he gave her 2 pints of whole blood and 1 pint of plasma.

The patient was a 28-year-old nulliparous, single white woman who clinically appeared very ill. Her last menstrual period was March 27, 1953, 10 weeks prior to admission. She was semicomatose, the blood pressure was 150/90, pulse 120, respirations 32, temperature 100.4° F., with a markedly distended abdomen and a small amount of bright vaginal bleeding. No bowel sounds were heard and there was evidence of fluid in the abdominal cavity.

Bimanual palpation revealed a soft, patulous cervix which admitted a fingertip and fullness in the cul-de-sac, but the corpus was not palpable because of the abdominal distention. With the speculum inserted, a small amount of bright and dark blood was noted coming from the cervical os and there were several small recent lacerations on the anterior cervical lip similar to those made with a tenaculum.



Fig. 1.—The black area shows the area of rupture, extending from the left uterine artery to the right cornu.

We felt that it was either a ruptured ectopic pregnancy or a criminal abortion with intra-abdominal hemorrhage.

She was taken to the operating room and a colpopuncture was done, with dark blood withdrawn in the syringe.

A midline subumbilical incision was made, and as soon as the peritoneum was open, approximately 1,500 to 2,000 c.c. of blood gushed out or was suctioned out from the cavity. The uterus was literally torn for a distance of 8 to 10 cm. from the right horn along the fundus around the left horn to the level of the left cervical vessel. The left tube and ovary were absent. The right tube and ovary were normal.

\*Presented at a meeting of the Chicago Gynecological Society, Dec. 18, 1953.

Due to the extent of the tear a hysterectomy was done. The cervix was not removed because of the patient's poor condition. The bowel was carefully examined for lacerations, but none were found. The abdomen was closed.

Her immediate postoperative condition was fair. The blood pressure was 110/70, pulse 134, respiration 20. By this time she had received 1,000 c.c. of whole blood and intravenous fluid therapy was continued. Streptomycin, 0.5 Gm., and procaine penicillin, 400,000 units were given every six hours. The following morning, with no oral nourishment tolerated and a fever of 101° F., pulse 126, and respiration 28, intravenous Terramycin was given (1.0 Gm. daily). The evening of the first postoperative day the patient was stuporous, temperature 104° F., pulse 120, with labored respirations resembling the Cheyne-Stokes variety, and the paralytic ileus was still present.

At this time, because of her very critical condition, 25 units of ACTH was given and continued at six-hour intervals.

The hospital course from here on was one of gradual improvement, the ileus disappearing on the second postoperative day the patient becoming afebrile by the fourth postoperative day.

She was discharged in good condition on the eleventh postoperative day. The follow-up examinations have shown her to be in excellent condition.

### Summary

A case is presented of a severely lacerated uterus following a criminal abortion with unusual preadmission circumstances.

30 NORTH MICHIGAN AVENUE



## SPONTANEOUS ANNULAR DETACHMENT OF THE CERVIX DURING LABOR

### A Case Report

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**S**INCE annular detachment of the cervix, occurring spontaneously during labor, is a rare and interesting complication, we are reporting an additional case.

Review of published articles reveals some 55 reported cases to 1947 (Ingraham and Taylor<sup>1</sup>). Since that time a review through 1950 reveals five additional cases reported by Finn<sup>2</sup> and a case by McMath.<sup>3</sup>

Ingraham and Taylor report that the first case in the literature was by Scott in 1821. They state the first case in the American literature was reported by Johnston in 1851. Finn reports 5 cases of spontaneous detachment in 56,884 deliveries at New York Hospital, making a total of 12 cases reported in the American literature to 1950. An additional case was reported from Fitzsimmons Army Hospital by Akers and Steele<sup>4</sup> at the Obstetrical-Gynecological Seminar at Brooke Army Hospital in March, 1952. We believe our current case to be the fourteenth reported in the American literature.

### Case Report

A 28-year-old gravida iii, para ii, white woman patient was admitted to William Beaumont Army Hospital on Oct. 29, 1953, in active labor. The membranes had ruptured. There were a bloody show, finger-tip dilatation and complete effacement. The presenting part was at minus 3 station. The fetal heart tones were good.

According to the past history, the patient's first child was delivered in February, 1943, after a 33½ hour labor. The male infant weighed 9 pounds, 8 ounces, and is living. Her second child was delivered in January, 1945, after an 18 hour labor. This male weighed 9 pounds, 10¾ ounces, and is living. Episiotomies were performed with each delivery. In 1945, an appendectomy and a Coffey-type suspension were performed. In 1946, a left salpingo-oophorectomy was performed for a left tubovarian abscess. In 1948 partial resection of a cystic right ovary was performed. The patient was first seen by us in 1951. Since that time and until her third confinement she had had two curettages performed by the senior author for menorrhagia. On each occasion the patient was studied for blood dyscrasia because of extensive vaginal bleeding not cured by curettage.

Her last menstrual period was Feb. 2, 1953, with an estimated date of confinement of Nov. 9, 1953. On April 5, 1953, the patient was admitted to the hospital with moderate vaginal bleeding, and treated as having a threatened abortion. The patient spotted on July 27, 1953, but did not report to the hospital until her next prenatal visit. Except for a 33 pound weight gain, her prenatal course was uncomplicated.

Bleeding was scant during labor. The patient complained of very painful contractions. Throughout labor the presenting part remained high, so that cervical dilatation remained in question. One hour before delivery the intern reported a blood clot at the introitus. The junior author examined the patient for the first time and found a protruding mass resembling a clot. The station was plus 2, and the dilatation was in doubt. An immediate decision was made to perform a sterile pelvic examination.

The cervix was found to be 2 cm. dilated, and completely detached except for a small portion which remained attached anteriorly. The fetal head was on the perineal floor. After a left mediolateral episiotomy, a normal female infant weighing 8 pounds, 9½ ounces, was easily delivered with outlet forceps. The third stage of labor lasted six minutes. The amputation of the cervix was completed by cutting the remaining 1 cm. attachment. Bleeding required a vaginal pack. The episiotomy was repaired.

By this time the patient had been crossmatched and preparation had been completed for immediate hysterectomy. Decision to remove the uterus was prompted by the continued bleeding. The pack was removed in the operating room and found to be saturated with blood. Hysterectomy was performed without difficulty.

The mother and baby had an uneventful course following operation and were discharged on the twelfth postoperative day.



Fig. 1.



Fig. 2.

Fig. 1.—Shows the patient on the delivery table. The cervix is almost completely detached and through the introitus. Note external cervical os, which remained about 2 cm. dilated.

Fig. 2.—This shows an internal view of the cervix. The internal os remained 2 cm. dilated. Note the large bleblike spaces. Microscopically these are thought to be vascular.

The pathologic report on the specimen is as follows:

**Gross.—A.** The detached piece of cervix which included the external os was dark bluish red in color. It measured 8.5 by 6.5 by 1.5 cm. The os measured 2 cm. in diameter. The entire specimen was suffused with blood. The detached surface was surprisingly smooth. On section there were numerous blood- and air-filled, smooth-walled spaces in the detached cervix. These appeared to be varices.

**B.** The body of the uterus measured 17 by 12 by 8 cm. The cervical canal was detached and formed a separate sleeve of tissue measuring 5 by 6 by 5 cm. The canal was 5 cm. in diameter. The uterus was obviously postpartum and the entire endometrial surface was hemorrhagic. No placenta remained. The site of attachment was apparently on the anterior wall and fundus.



Fig. 3.

Fig. 3.—Microscopic view of distal end of cervix showing large vascular spaces, acute inflammation, and hemorrhage.

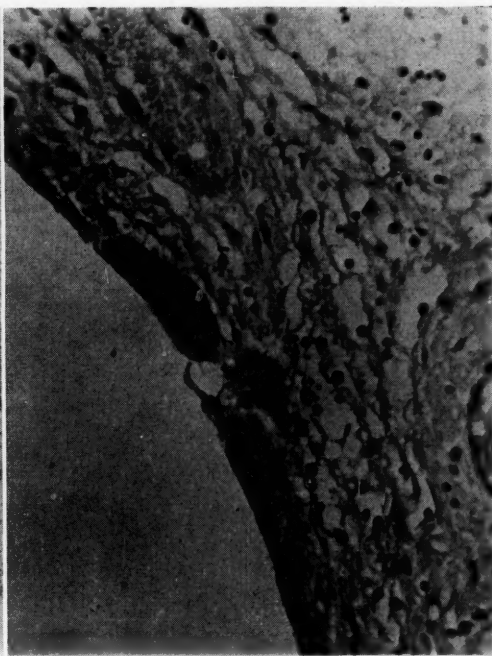


Fig. 4.

Fig. 4.—Microscopic view showing trophoblasts lining vascular spaces.

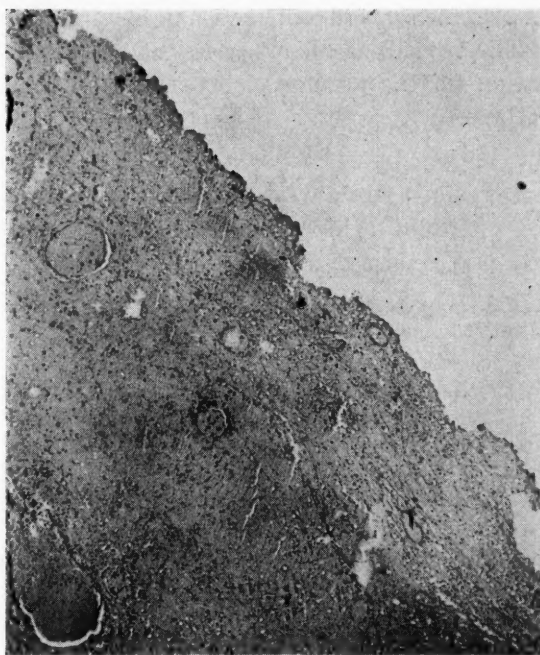


Fig. 5.—Microscopic view of upper or torn edge of cervix. Note sharp line of tear, big blood spaces, hemorrhage, and absence of muscle.

*Microscopic.*—A. The epithelium was moderately hyperplastic. The cervix was edematous and hemorrhagic with a diffuse polynuclear infiltrate. There were two changes that were quite striking. The first was the absence of muscle and the second was the cystic spaces seen grossly. These spaces were lined by a serous coagulum and giant cells. It was suspected that the spaces were telangiectatic vessels, but this could not be proved. The giant cells appeared to be trophoblastic.

B. The uterus was obviously immediately postpartum. There was a pronounced invasion of the myometrium by trophoblastic cells. Occasional vessels were invaded and there were some vessels with very thick walls.

*Diagnoses.*—Annular detachment of the cervix. Postpartum uterus.

### Comment

There are multiple possible explanations for the detachment. The most likely is varices with scarring and trophic changes complicated by erosion and lysis by invading syncytial cells of the trophoblast. The consequent weakening resulted in detachment.

In retrospect we have pondered the necessity for removal of the uterus in this case, but feel that the amount of bleeding encountered made this the only reasonable course of action.

Our own critical comment would of necessity include the statement of regret that a sterile pelvic examination was not performed earlier in this patient's labor. We were dealing with a multipara, with a proved pelvis, however, and there was no indication during her labor of what was happening to the cervix.

Previous authors have given primiparity, cephalopelvic disproportion, and prolonged labor as the predisposing causes of cervical detachment. None of these criteria were present in this case.

We believe that organic structural changes present in this cervix predisposed to its detachment. The varices or blood spaces, as described by the pathologist, may be the explanation for the previous menorrhagia which did not respond to dilatation and curettage.

### Summary

A case of spontaneous annular detachment of the cervix followed by hysterectomy during a patient's third labor has been reported. This is believed to be the fourteenth case reported in the American literature.

We wish to express our appreciation to Major Hurston Heslington for the description of the gross specimen and microscopic diagnoses.

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## **CICATRIX AND ATRESIA OF THE CERVIX OF UNKNOWN ETIOLOGY COMPLICATING PREGNANCY**

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### **A Case Report**

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**W**E ARE reporting a rare and interesting condition of a cicatrix of the cervix with atresia complicating a postmature pregnancy. This condition was not diagnosed until the patient had gone two and a half months past her estimated date of confinement, and the fetus was known to have been dead for one and a half months.

We believe every patient should have a pelvic examination when first seen, no matter how near she is to the estimated date of confinement. This should include visualization of the cervix. The question arises, when should induction be considered with a missed labor?

### **Case History**

This 30-year-old gravida iv, para ii, was first seen in the Obstetric Clinic on Sept. 2, 1953. She stated that her last menstrual period occurred on Dec. 8, 1952. This visit, 13 days prior to the expected date of confinement, was her first prenatal examination with this pregnancy. Past history revealed that she had delivered an 8 pound infant on Nov. 21, 1946, and an 8 pound infant on April 29, 1949. These deliveries were spontaneous and uncomplicated. The cervix was cauterized in her doctor's office following each confinement. Her third pregnancy resulted in an early spontaneous abortion in March, 1951. No dilatation and curettage was done. At the first visit of her fourth pregnancy, her weight and blood pressure were within normal limits. The fetal heart rate was 140. Vaginal examination was not done because the examining physician considered her too near term. Her second visit, one week later, revealed a 4 pound weight gain and slight ankle edema. Blood pressure, urinalysis, and fetal heart rate were normal. She did not return to the clinic until Oct. 22, 1953, or five weeks past the expected date of confinement. She reported that she had not felt life for one week. Fetal heart tones were not heard. X-ray examination of the abdomen showed evidence of fetal death (Spalding's sign). It was agreed by the attending physicians to allow the spontaneous onset of labor. The fetal head was dipping into the pelvis, but engagement had not taken place. On Nov. 5, 1953, the patient was observed in the hospital with uterine contractions. These stopped and she was sent home. Her general condition remained satisfactory. Her blood pressure and weight remained the same. On Dec. 4, 1953, ten weeks past her expected date of confinement, the patient was admitted for induction of labor. Sterile pelvic examination revealed the absence of an external cervical os. The cervix felt firm and was covered with an intact mucosa. In the operating room, repeat vaginal examination substantiated the findings. At cesarean section a markedly hypertonic uterus was observed. The amniotic fluid escaped under increased pressure through the uterine incision. A macerated infant was delivered. The placenta was free in the uterus, and was markedly calcified and fibrotic. While the uterine incision was open no internal cervical os could be found. Panhysterectomy was then performed. Examination of the specimen removed

revealed no evidence of a cervical canal. The patient's postoperative course was complicated by fever up to 104° F. during the first 96 hours. She required four units of bank blood during operation and in the immediate postoperative period. There was no evidence of afibrinogenemia. She was discharged from the hospital on the eleventh postoperative day.

The pathological report follows:

*Gross.*—The specimen consisted of a uterus which weighed 743 grams and measured 17 by 10 by 10 cm. The uterine wall measured 2 cm. in thickness in the fundal region, 1 cm. in the lower uterine segment. The organ was lined by a thick, green, stringy membrane which could be scraped out, revealing a deeper yellow spongy layer. The internal cervical os and the external cervical os had been obliterated. Several small, yellowish, rubbery masses, measuring 1.5 by 1 by 1 cm., remained at the former site of the cervix. The area of cervical atresia was cut with marked resistance, revealing a wall of dense, white, firm tissue.

*Microscopic.*—Many sections taken through the small fragment of the external cervical lip presented a layer of thickened pavement epithelium under which there were loose fibrous tissue and dilated vessels and lymphatics. There was a diffuse infiltration of lymphocytes and histiocytes. The deeper tissues showed dense sheets of hyalinized collagen separating muscle bundles. There were focal clusters of lymphocytes. The vessels were partially surrounded by the latter and contained thickened walls. Serial sections through the region presented no discernible remnants of endocervix or cervical canal. Sections through the uterine wall from the fundal region presented fibrosed chorionic villi with an abundant calcium deposit between the separate villi. Deeper in the section one found hyalinized decidua, remnants of chorionic villi, large blood sinuses, and persistent flecks of calcium. Polymorphonuclear leukocytes were found abundantly around the necrotic elements.

*Diagnosis.*—Uterus and cervix: Cicatrix of cervix with atresia.

### Comment

The diagnosis of atresia of the cervix was made at the time of the first pelvic examination. It is a foregone conclusion that the cervix was patent at the time of conception. When atresia occurred is not known.

This patient sought no prenatal care until two weeks prior to the estimated date of confinement. The practices of (1) no pelvic examination for one month prior to an expected date of confinement, and of (2) allowing patients with fetal death in utero to go into spontaneous labor were adhered to in this case. These practices caused delay in diagnosis and treatment in this patient.

Norris<sup>1</sup> (quoting Curtis<sup>2</sup> and Cooke<sup>3</sup>) has summarized the etiological factors which could cause stenosis and lead to atresia of the cervix in the nonpregnant uterus. These are reviewed here, since one or more of the following could explain cicatrix of the cervix with atresia in a pregnant uterus. While the etiology in our case is unknown, the following will give basis for speculation.

Norris lists these factors:

#### I. Following therapeutic procedures.

1. Electric cautery for cervicitis and endocervicitis.
  - a. Treatments too often repeated.
  - b. The electric tip at too great a heat.
2. Chemical cautery.
  - a. Too frequent treatments with silver nitrate or other tissue caustics.
3. High frequency "radio conization" of the cervix for endocervicitis.
4. Curettage, in cases where the cervical canal has been vigorously curetted.
5. Operations on the cervix. Various types of trachelorrhaphy.

Fig. 1.



Fig. 2.

Fig. 1.—Shows the site of the previous external cervical os, covered with intact vaginal mucosa.

Fig. 2.—Shows a view looking down from within the uterine cavity showing absence of internal cervical os. The portion of the photograph in critical focus demonstrates the pathological condition.

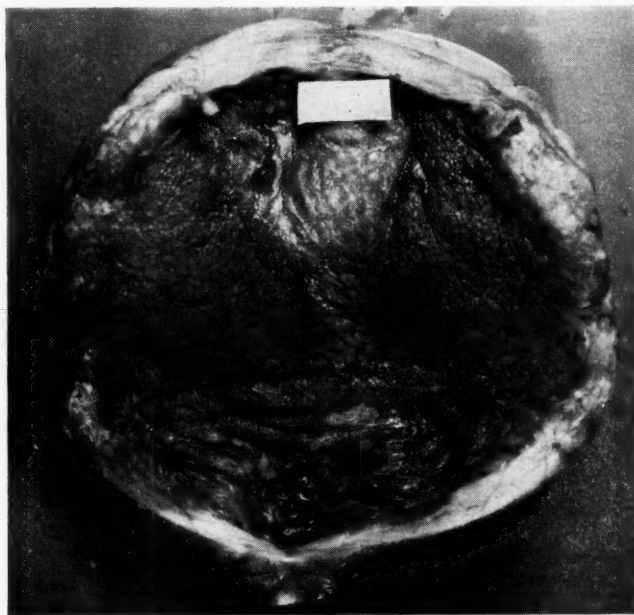


Fig. 3.—Shows a view of uterus and cervix, with complete atresia and cicatrix of the cervical canal. Note the thickness of the occluded canal.

## II. Following attempted abortion.

1. Instrumentation.
2. Insertion of chemicals into the cervical canal—as potassium permanganate tablets.

## III. Following natural causes.

1. Spontaneous healing of badly lacerated cervixes with endocervicitis.
2. Senile atrophy of cervical mucosa.
3. Growth as (a) fibroids in cervical area, (b) carcinoma of the cervix.

In the literature we found two similar cases of cervical atresia complicating pregnancy. One case was reported by Bowles<sup>4</sup> and the other by Estanga.<sup>5</sup> The case reported by Bowles was diagnosed after prolonged labor with no cervical dilatation. The patient was delivered of a living child by low cervical cesarean section, following which an artificial cervical opening was made. The patient had painful menstrual periods afterward, and required several dilatations of the "cervical canal." The patient of Estanga had had two previous vaginal deliveries. There was no history of infection or instrumentation to account for the complete occlusion of the cervix. Estanga was unable to offer any explanation. He delivered his patient by vaginal cesarean section.

We are aware that there was undue delay in the diagnosis and treatment of this case. We feel that an error was made in not performing a sterile pelvic examination at the time of the initial visit. The patient failed to return to the clinic for five weeks. At the time of her next visit, the fetus had died.

After questioning the patient we were unable to find an explanation for the atresia. From the pathological report, we feel that infection played a major role. We are unable to substantiate this by history or clinical manifestations. The patient denied any attempt at instrumentation or insertion of chemicals into the cervical canal to produce abortion during this pregnancy. The only etiological factors that can be suggested are (1) chronic cervicitis and endocervicitis, (2) electrocautery of the cervix following her previous vaginal deliveries. Neither of these was able to produce atresia to prevent conception, nor to cause the patient any degree of dysmenorrhea. It is suggested that pregnancy was the added factor needed to produce the atresia.

### Summary

1. A case of cicatrix of the cervix with atresia complicating pregnancy, treated with cesarean panhysterectomy, is reported.
2. Review of the etiological factors known to cause atresia of the cervix in the nonpregnant uterus is given.
3. Pelvic examination (sterile if necessary) and visualization of the cervix should be done at the time of the patient's first visit, no matter how near the expected date of confinement.
4. Review of the literature shows this to be a rare complication of pregnancy.

We wish to express our appreciation for the pathological report to Lieutenant Colonel Alfred S. Blauw, MC, USA, Department of Pathology, William Beaumont Army Hospital, Fort Bliss, Texas.



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## AN UNCOMMON COMPLICATION FOLLOWING THE USE OF THE MILLER-ABBOTT TUBE

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IT HAS been demonstrated that intestinal intubation, a very advantageous procedure in most cases both of paralytic and mechanical bowel obstruction, may be dangerous even when properly handled. Smith,<sup>1</sup> Chaffee,<sup>2</sup> Kleinsasser,<sup>3</sup> and, more recently, Lichtenstein,<sup>4</sup> reporting on personal observations, referred to such complications and, with an explanation of the causes, offered suggestions as to the best way to obviate them.

The inability to withdraw the balloon-tipped tube, as in the case to be presented, is a complication which occurs with a certain frequency and which may be due to several causes. The most common ones are: (1) knotting and coiling of the tube; (2) distention of the balloon; (3) passage of the tip through the ileocecal valve.

Cases of knotting of the tube in the jejunum have been reported by Brenizer<sup>5</sup> and by Madigan,<sup>6</sup> in which a laparotomy was necessary. In a statistical study of 1,000 cases of intestinal intubation, Smith<sup>1</sup> reported knotting of the tube as occurring ten times. Herrera<sup>7</sup> reported a case of knotting of the tube, which passed spontaneously through the anus. In a case mentioned by Lichtenstein<sup>4</sup> the tube, released in order to avoid retrograde intussusception which might have been caused by pulling the tube up, was found at the operation coiled just against the ileocecal valve.

Moore<sup>8</sup> reported a case of overdilatation of the terminal balloon with gas, producing complete intestinal obstruction necessitating a laparotomy. In order to avoid such a complication, Cantor<sup>9</sup> suggested the use of a balloon made of Neoprene G, which is only 19 per cent as permeable to carbon dioxide as is latex rubber. Harris<sup>10</sup> reported three cases of difficulty in removing the tube because of the increase in amount of gas in the bag, in one of which a laparotomy was necessary.

When the tip of the tube passes through the ileocecal valve, Harris,<sup>10</sup> who reported seven such cases, advised cutting it at the nares and allowing it to be eliminated by anus or colostomy. Sometimes such a procedure is not sufficient, as occurred in the case reported by Kleinsasser,<sup>3</sup> when the tube, cut at the nares, was found at the operation coiled in a distended loop of ileum, with the tip in the ascending colon.

In case of difficulty in withdrawing the tube, rough and too strong traction on it can cause further serious complications, as in a case of Harris,<sup>10</sup> when this procedure caused a tear of the bowel with production of a localized abscess. Another problem is associated with the known fact that the small bowel may become pleated on the tube, leading to intussusception.

The following case report is interesting not only as an example of an unusual complication following intestinal intubation, but also because in this case the Miller-Abbott tube was applied before an abdominal operation, as a prophylactic measure against a possible postoperative intestinal obstruction.

### Case Report

A 53-year-old Negro woman was admitted to the hospital on Dec. 1, 1953, with the chief complaint of vaginal bleeding of approximately two years' duration, with left leg pain and slight venous distention in the same limb. A diagnosis of carcinoma of the cervix, Stage III, was made and an exploratory laparotomy, possibly to be followed by a pelvic exenteration, was planned. The neurologist had referred the pain in the left leg to extension of the malignancy to the lateral pelvic wall, without signs of sacral plexus involvement. Work-up, however, revealed obstruction of the left ureter.

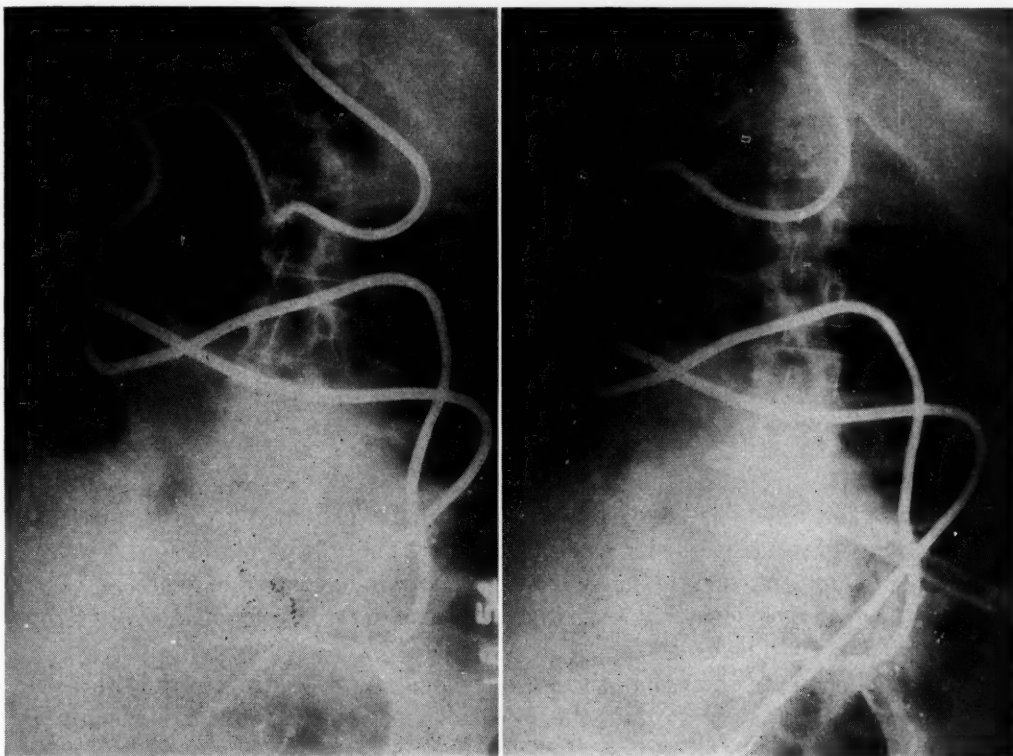


Fig. 1.

Fig. 2.

Fig. 1.—Tube released. Note the angulation in the lower left quadrant.

Fig. 2.—The tube is under traction. Note the persistent angulation in the lower left quadrant.

Two days before the operation, as is routine for such procedures, a No. 18 Miller-Abbott tube was passed very easily. Ten hours later the tip was beyond the pylorus, and when the operation was started, on Jan. 4, 1954, the mark at the nares was four feet. A pelvic exenteration was performed under hypotensive anesthesia. Upon division of the rectosigmoid, the Miller-Abbott tube was encountered and cut. The tip of the tube with the balloon was removed with the specimen. Holes were made on the sides of the distal portion of the tube and it was pulled up by the anesthetist to a point which registered the three-foot mark at the nares.

The postoperative course for the first two days was characterized by slight abdominal distention and no bowel sounds were audible. Electrolyte balance was normal and the general condition was good. On the third postoperative day the patient started to vomit and the abdomen became more distended. The Miller-Abbott tube was draining some dark fluid.

On the fourth postoperative day the tube, left free, was still at the same position. A rectal tube, put through the colostomy, did not drain. Signs of intestinal obstruction developed, with moderate abdominal distention, increased vomiting, and deteriorating general condition. The tube, completely released, failed to proceed downward.

Firm traction applied at this time to the upper end drew the tube up to the two-foot mark, but at this point the tube seemed to be firmly immovable. Under fluoroscopy it was noted that the tube, under traction, was fixed somewhere in the left lower abdomen (Figs. 1 and 2). The impression now was that an adhesion was retaining the tube at the point where the film showed it to be fixed, or that the pulling on the tube had caused a reverse intussusception, with eventual bowel damage.

On the fifth postoperative day it was decided to carry out an exploratory laparotomy. On the operating table a volvulus was found with the loop of inverted bowel containing the tube held down by the mesentery of the sigmoid used for the colostomy. Superiorly, a small tear of the mesentery was also noted. The bowel was slightly congested and dilated. The obstruction was relieved with some difficulty owing to the relative rigidity imparted to the loop of obstructed bowel from the tube within it. No resection was needed, however, and the Miller-Abbott tube was withdrawn up to a safe level. Bowel movements occurred on the day after this operation and the patient made a good immediate recovery.

### Comment

In our case the preoperative insertion of the Miller-Abbott tube failed to prevent and perhaps contributed to the intestinal obstruction. On the other hand, the tube permitted the identification and location of the cause of the initial obstruction, with consequent prompt solution of the problem.

As far as the original application of the tube was concerned, the position of the tube was not followed carefully and often enough under fluoroscopy. Such study has been constantly advised, in order to prevent the tube from going too far down. The tube was inserted too early and its proximal tip was not fixed, so that it progressed by itself too far. At the time of the operation the tube, instead of being cut, should have been withdrawn beyond the ileocecal valve. This has been suggested by many writers who encountered difficulties in drawing it back when the tip became stuck over the valve.

In conclusion, on the basis of this experience and according to the literature on this subject, we suggest that the Miller-Abbott tube should not remain in situ too long and that its position must be checked often by x-ray. In the event the tube cannot be pulled up, and if its tip is not beyond the ileocecal valve, a laparotomy is to be strongly considered, as its lack of progress may be an early sign of mechanical intestinal obstruction.

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## A PROCEDURE TO REDUCE PERINEAL DISCOMFORT IN THE PUERPERIUM

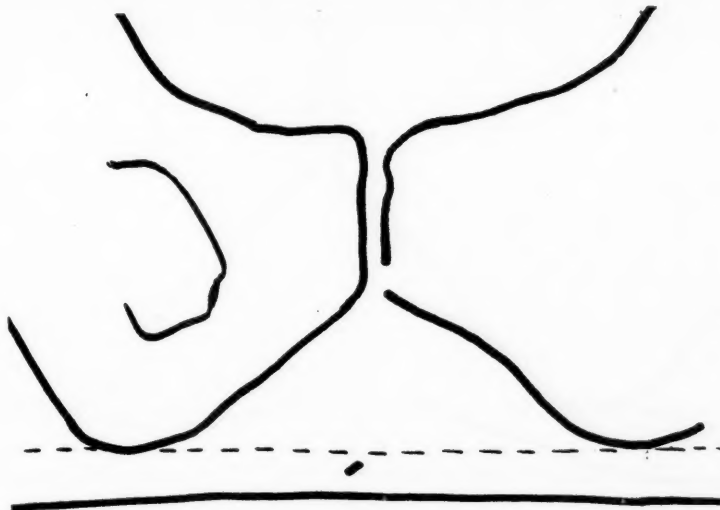
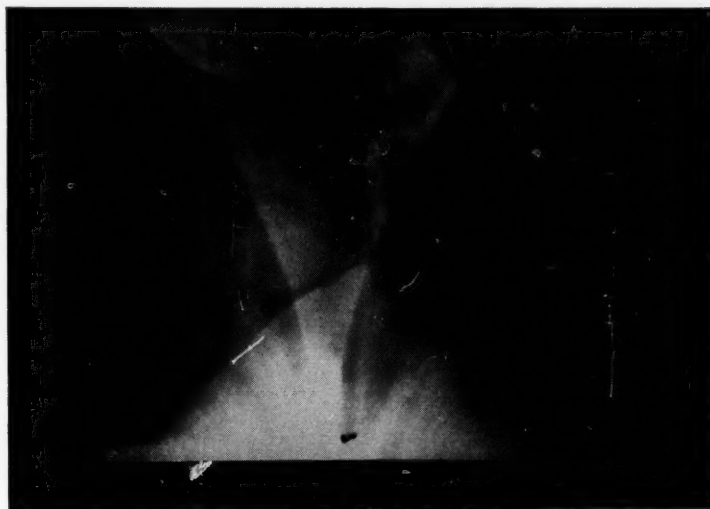
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**P**ERINEAL discomfort in the puerperium is often mentioned, but little is said about its relief.

For several years I have observed that the patient who has had an episiotomy will instinctively go to the softest chair available. If there is none, she will place a pillow on a hard chair in an attempt to get relief. Unfortunately, her soreness persists or becomes worse.

A.



B.

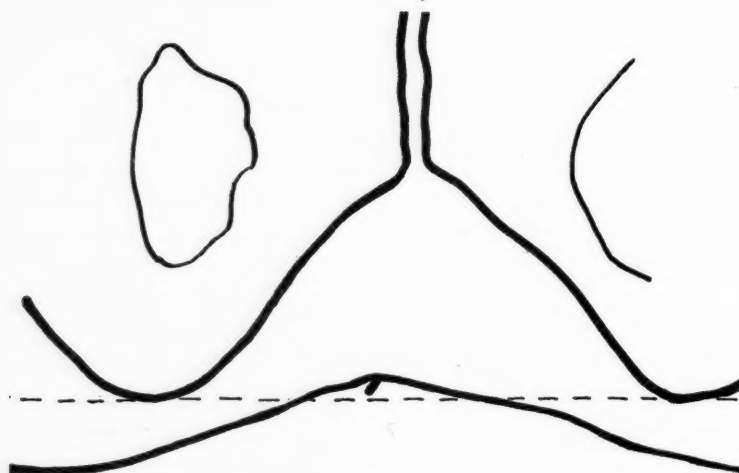
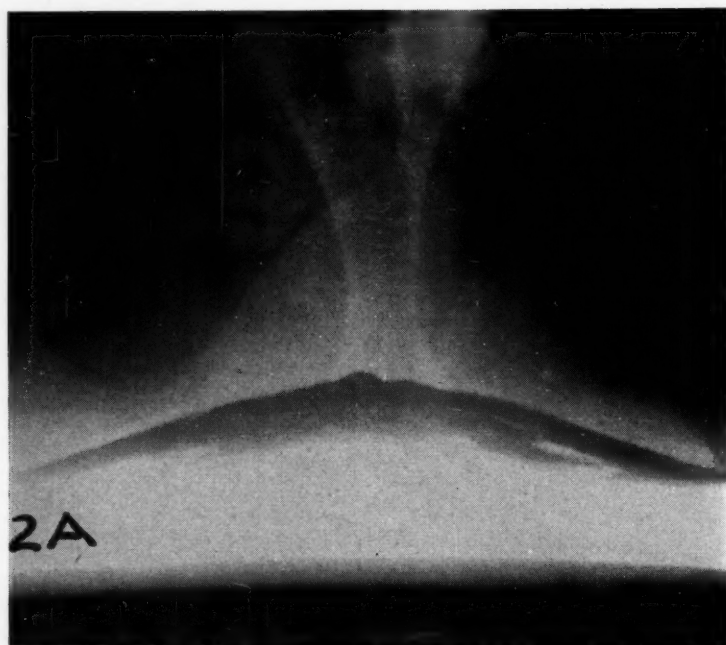
Fig. 1.—A, Shows x-ray of patient with wire in place, sitting on hard chair. The wire is above the surface of the chair.

B, Outline drawing of A.

I have learned that she will be more comfortable if she sits only on hard-surfaced chairs.

Fig. 1, A shows a patient model who has had a piece of wire placed along the perineum, as if for a midline episiotomy. It is held in place by adhesive tape, and she is seated upon a metal stool. It can be clearly seen that the wire is above the surface of the stool, and slightly below the level of the ischial tuber-

A.



B.

Fig. 2.—A, Shows same patient sitting on deep cushion covered with barium. The cushion is forced upward displacing the wire marker, which is obscured by the barium.  
B, Outline drawing of A.

osities. In the sitting position the ischial tuberosities bear all of the body weight, and the perineum is suspended at about their lowermost level. The hard-surfaced stool cannot rise up in the midline to press upon the episiotomy and cause pain.

Fig. 1, *B* is an outline drawing of Fig. 1, *A* to clarify this point. The dotted line shows the level of the ischial tuberosities.

Fig. 2, *A* shows this same patient, the wire still in place, seated upon a deep cushion. To demarcate the surface of this cushion clearly, a coating of barium was placed between two layers of aluminum foil. This sheet of foil was placed over the cushion. When the patient sat down, the ischial tuberosities sank deeply into the cushion. The latter moved up between the ischial tuberosities to such a degree that it pressed against and forced the wire, representing the episiotomy, upward in the midline. The wire in Fig. 2, *A* is obscured by the barium and foil. Such a patient would experience great discomfort.

Fig. 2, *B* is an outline drawing of Fig. 2, *A* to clarify the x-ray further. The wire, not seen in Fig. 2, *A* and foil covering the cushion are high up, above the level of the ischial tuberosities as represented by the dotted lines.

I have had sufficient experience with patients using hard chairs to prove that they are more comfortable.

I wish to acknowledge gratefully the cooperation and suggestions of Dr. Harry Fishbein, Roentgenologist.

## AN OBSTETRIC FORCEPS FOR THE ROTATION OF THE FETAL HEAD

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THE persistent occiput posterior position of the fetal head continues to be a problem in the delivery of the baby. The present-day methods for handling the condition are: to deliver the head as an occiput posterior, to do a manual rotation, version, cesarean section, or to use Kielland forceps or the Scanzoni maneuver. The limitations of each procedure are discussed in the textbooks. Kielland forceps, a favorite with many obstetricians, have been abandoned by us many years ago. The technique, as described by Kielland, of introducing the anterior blade into the uterus and rotating it inside the uterus is a dangerous procedure.

In recent years the management of deliveries has changed. We no longer attempt delivery of a head high up in the pelvis, or unengaged or poorly engaged, or fixed in the midpelvis, as this is a damaging procedure to mother and baby.

When the head is in the occipitoposterior position it may rotate to an anterior and be easily delivered spontaneously or by low forceps. When it does not rotate spontaneously we have to do the rotating. When the head is down at the floor of the pelvis, it is illogical to displace the head upward as has to be done by the Kielland forceps or by manual rotation.

The Scanzoni maneuver is the method we prefer; but in doing the rotation we were obliged to use forceps whose shape, size, and general construction were intended for making traction on the baby's head. When the Elliot or Simpson forceps are used to do the rotation, the tips of the blades cut and tear the vaginal wall. By rotation of the handles through a large arc this is partly overcome, but in the process the head is displaced and the sides of the blades hit up against the walls of the pelvis and interfere with the rotation.

Because the occipitoposterior position is a serious problem, I have devised the forceps illustrated in Figs. 1 and 2, which simplify the rotation of the baby's head.\* The special feature of these forceps is that the tips of the blades have been shortened, making the blades 35 to 40 mm. smaller than those of the standard traction forceps. This eliminates the parts that cut into the vaginal wall. The forceps as a whole are lighter in weight, the blades are narrower, and there is less of a pelvic curve. The lock is of the pivot and notch type. The bar on the end of the handles is for the purpose of locking the forceps after they are applied to the head. By this means the forceps hold the head snugly and prevent its being compressed, and at the same time prevent the forceps from rotating around the head. The screw locks the bar in place; it also serves to indicate the convex side of the pelvic curve. This bar, together with the crossbars below the lock, is for the fingers to hold the forceps and rotate them in the required direction (Fig. 2).

The application of the forceps is simple. The left blade is always introduced first and then the right blade, and a correct cephalic application is attained. The bar at the end of

\*Sold by O & G Instrument Co., New York 19, N. Y.



the handles is locked, to hold the head snugly. The forceps are rotated through a small arc to turn the occiput anteriorly. For the rotation of the head with these forceps, very little anesthesia is needed. We use ether, the open-drop method, because it is the simplest and safest. A few drops of ether are given and the rotation is completed in less than a minute, while the patient is still under first-stage anesthesia. The ether is stopped, the forceps are held in place for a while to allow the head to get set in its new position, and then the forceps are removed. If the woman has strong pains, and especially if she is a multipara, the baby will be expelled spontaneously. The rotation forceps are not intended for traction. When she does not deliver the baby by herself, more ether is given, traction forceps are applied, and the baby is extracted. If after rotation of the head to the anterior position the head is still within the pelvis, above the perineum, we prefer to use the Tarnier axis-traction forceps to complete the delivery. The mention of the Tarnier axis-traction forceps suggests a head that is not engaged and a difficult delivery; this is not necessarily the case, as we find their use of great help in the routine delivery of any head that is above the perineum. We consider the Tarnier forceps the only true axis-traction forceps. Our Tarnier forceps have been made less bulky, with a simpler traction handle which makes application and traction easier.

When the head is in transverse arrest in right occipitotransverse or left occipitotransverse position, a cephalic application is made by inserting the left blade first and wandering the

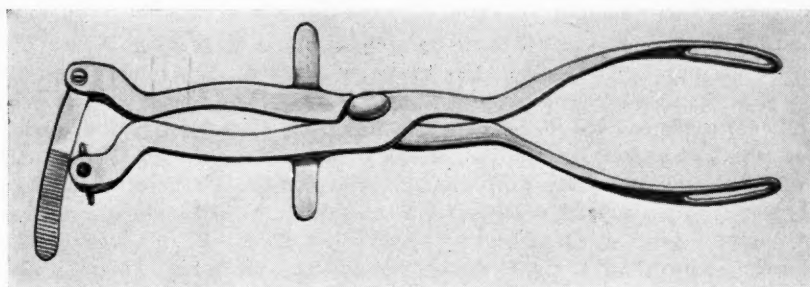


Fig. 1.—The forceps. The blades are shorter, narrower, and lighter than those of the standard forceps; shank; pivot and notch lock; bars for rotation; handles; safety and rotation bar, and screw to lock the bar.

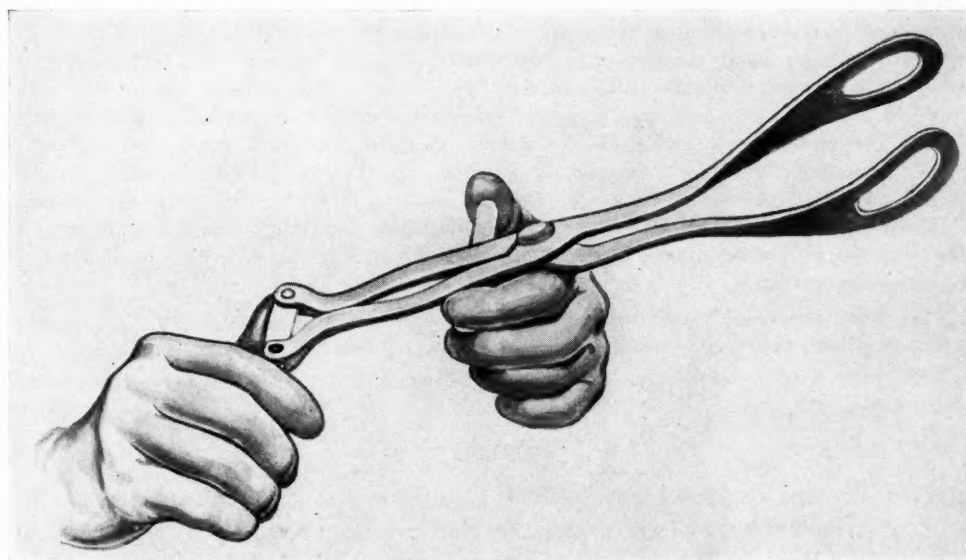


Fig. 2.—The forceps as they appear when applied to a head in the right occipitoposterior position; and showing the hold on the forceps by the fingers, ready for rotation.

second blade into a correct cephalic position, and then rotating the head anteriorly. If the head drops back to its original posterior or transverse position when the forceps are removed, the rotation forceps are reapplied and the head is rotated to the anterior position again, but now one blade at a time is removed and replaced by the blades of the traction forceps. When the traction forceps are in proper position with the occiput anterior, then the delivery is completed. We do right mediolateral episiotomies in nearly all our deliveries. We never do a median episiotomy, and thereby avoid third- and fourth-degree lacerations.

Even when the head is in the left occipitoanterior or right occipitoanterior position but not directly anterior, we use the rotation forceps first, to bring the head directly anterior, which then makes a cephalic application of the traction forceps easier.

In making the diagnosis of the position of the head, the textbooks describe the shapes of the anterior and posterior fontanels, and point out that the anterior fontanel is larger than the posterior. These signs become obscured in labor and the fontanels cannot be differentiated. A positive way of determining the position is by noting the fact that the anterior fontanel has three sutures (2 coronal and 1 frontal) coming away from it, while the posterior fontanel has only two (lambdoidal) sutures. This can easily be palpated by passing one or two fingers over whatever fontanel is more accessible. We do not have to search for an ear, which necessitates dislodging the head, to determine the position. Incidentally, we conduct all labors by doing vaginal examinations in all stages of labor, as frequently as we deem them necessary, and thereby avoid the mistakes that are made from rectal examinations.

The posterior position is not a cause of prolonged first stage when it is not associated with disproportion or uterine inertia. The posterior position will prolong the second stage if the head does not rotate promptly when it reaches the pelvic floor, at which station rotation normally takes place. We therefore try to bring the head down to the pelvic floor for spontaneous rotation or for rotation by forceps. The woman is encouraged to bear down when the cervix is fully or nearly fully dilated. We give her 3 minims (2 units) pituitary extract intramuscularly every 20 minutes for 2 to 3 doses, to stimulate uterine contractions and help the uterus bring the head down to the pelvic floor. At this station of the head it becomes a simple procedure to rotate the head and deliver the baby. The fetal heart should be auscultated frequently during the second stage. The nurse listens to the fetal heart after each pain. When the fetal heart slows down to less than 100, immediate delivery is imperative.

There is one precaution that must be observed. The forceps are applied very easily, but we must make certain that the tips of the blades are inside the cervix. This is done by passing a finger along the blades to feel their tips inside the cervix. If the tips of the blades impinge on the outside of the cervix they will cut off a circular rim of the cervix. After delivery there will be found a ragged tongue-like piece of cervix hanging down in the vagina. Fortunately, it is not a serious matter. It should be left alone, no attempt should be made to suture it back in place, nor should it be cut off. There is no bleeding from this torn end. It should not be mistaken for retained placenta or membranes. The vagina should be packed with gauze, which is left for twelve hours, so that this tissue does not hang out from the vagina. On examination a few days later no sign of the tear can be seen and the cervix appears normal.

We have also used these rotation forceps to convert a mentoposterior into a mentoanterior position; and a face presentation into a head presentation.

We have used these forceps in hundreds of cases and find them so useful as to be indispensable.

### Summary

New forceps designed especially for rotating the baby's head from a posterior or transverse position to an anterior position have been presented and described.

The application of the forceps is simple and the results are gratifying.

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1831 GRAND CONCOURSE

## BRAIN TUMOR SIMULATING PREGNANCY

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**P**RESSURE on the hypothalamus in women leads rapidly to amenorrhea, according to Morgan.<sup>1</sup> It is an established principle among many neurologists that bitemporal headache accompanied by sudden unexplained amenorrhea is brain tumor until this diagnosis is ruled out. Such amenorrhea accompanied by a positive laboratory test for pregnancy, however, is something new. The following case, therefore, may be of interest.

A 20-year-old woman was admitted to the hospital because of a progressive mental obtundity and loss of weight. She was also reported to be three months pregnant.

Her present illness had begun about three months previous to admission with severe, intractable headaches. Since this girl had been having marital difficulties and had had a "nervous breakdown" at age 16, an original diagnosis of tension headache was made. Six weeks before admission she began to vomit. The breasts and the uterus were found to be enlarging. A Friedman test was positive. Interestingly, a rat test, done as a check at the same time, was negative, but in view of the other findings was discounted. When the patient became exceptionally drowsy and neglectful of her duties about the house, it was supposed that she resented the "pregnancy" because of her misunderstandings with her husband. As Soniat<sup>2</sup> has pointed out, "hypersomnolence may be produced by tumors involving the floor of the third ventricle; such somnolence is frequently mistaken for narcolepsy or hysteria." So suggestive was the history of hysteria, that any other diagnosis was dismissed for a six weeks' period. At the end of this time the patient was completely bedfast and comatose.

On arrival at the hospital she would take small amounts of food, if fed, but otherwise showed no awareness of her surroundings. There was no measurable papilledema. There were no localizing signs, but a bilateral Babinski and ankle clonus were present. Spinal tap showed a total spinal fluid protein of 325 mg. per cent. The blood pressure was quite low, ranging between 70/50 and 90/60. There was no sugar in the urine. A carotid angiogram was done which showed a deformation of the carotid siphon compatible with a suprasellar tumor. While the films were still under discussion, the patient suddenly died. She was not pregnant.

The autopsy report described a deep purplish tumor 2 cm. in diameter lying between the optic chiasm and the cerebral peduncles. Microscopically there were areas of hemorrhage and necrosis, but tumor cells could be distinguished and appeared to be composed of different elements. There were some cells with small, dark nuclei and indistinct cell borders. Other cells were very large and contained very large vesicular nuclei with scant protoplasm. The tumor tissue in these areas nearest the hypothalamus was said to resemble chorionepithelioma. Sections taken of the pituitary were said to show neoplastic invasion of the anterior portion of the gland by single large tumor cells with deeply staining basophilic nuclei and darkly stained cytoplasm with indistinct borders. Other cells resembling lymphocytes were noted. In this area the tumor cells were thought to resemble pinealoblastoma. The final diagnosis was teratoma.



### Summary

Tumors pressing on the hypothalamus may cause amenorrhea and hypersomnolence. That they may also result in a positive Friedman test for pregnancy is shown by the case reported here. Further investigation of the Friedman test in such tumors may be of interest.

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## **A QUICK METHOD OF CIRCUMCISION**

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**T**HROUGH the centuries the operation of circumcision has been done by various methods. The advantages of the method described herein are that it is easier, believed to be safer, with less blood lost and less time consumed, and it is less painful to the child than many other methods. This method can be used on an infant or a child.

Since the description of immediate circumcision of the newborn by Miller and Snyder<sup>1</sup> was published, that method, too, has been tried and the advantages claimed have been confirmed.

### **Materials Needed**

One mosquito hemostat, curved or straight  
Plastic teaspoon with a slit in the tip longitudinally 2 mm. wide and 18 mm. long (may be made with an ordinary carpenter's saw)  
Sterile gauze and petrolatum dressings  
A cutting current machine

### **Method**

The foreskin is cleansed, dilated with the hemostat, retracted carefully posterior to the corona, recleansed, then replaced to normal position. A hemostat then clasps the protruding skin at the mucocutaneous junction so as to stretch the skin and the mucous membrane together. It is important in picking up the tip to place slightly more tension on the mucous membrane than on the skin; otherwise after the incision one will find an excess of mucous membrane. Retracting the skin on the sides with the fingers as one grasps the tip will help to obviate improper proportions.

Once the junction is grasped, the slit in the plastic spoon is fitted over the tip. The amount of tension to be placed on the hemostat and the angle at which the spoon should be held will be determined by the amount of material it is necessary to remove.

With a very fine electrode and cutting current adjusted to the lowest point at which the electrode will sever tissue, the needle severs the skin and mucous membrane distal to the plastic spoon.

No sutures are needed. A very adequate dressing is petrolatum gauze and plain gauze.

There rarely is any bleeding if the current used is the least amount capable of effecting an incision. In about 96 per cent of cases there is absolutely no blood lost.

Should there be an excess of mucous membrane after the portion distal to the spoon is removed, it is because the skin was not adequately retracted before picking up the tissue with the hemostat for removal. In that case, it may be beneficial to make a dorsal slit in the mucous membrane back to the corona.

### **Reference**

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# Department of Reviews and Abstracts

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EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

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## Review of New Books\*

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**The Management of Endocrine Disorders of Menstruation and Fertility.** By Georgeanna S. Jones. 198 pages with 37 illustrations. Springfield, Ill., 1954, Charles C Thomas, Publisher. \$5.75.

One of the most important aspects of endocrinology and gynecology is dealt with in this small book of one hundred ninety-eight pages. Although it is not a large work, the subject is quite adequately covered in a concise manner. The different hormones concerned with menstruation are discussed, including the different methods of assay, and explained in the light of present-day thinking. The mechanism of normal menstruation is described and then the abnormal conditions are discussed as to etiology and treatment.

This is all done in rather simple terms without bombast. It is thus easy to read and digest.

The newer concepts of gynecologic endocrinology are given, and considerable space is devoted to the role of the adrenal cortex.

**Hemorrhage in Late Pregnancy.** By John S. Fish. 180 pages with 22 illustrations. Springfield, Ill., 1954, Charles C Thomas, Publisher. \$5.50.

The laudable pregnancy salvage realized in recent years has not been accomplished by a proportionate elimination of all the contributory factors. Hemorrhage is now the most common cause of fetal loss and is frequently primary or at least an important secondary factor in many other maternal or fetal deaths. The three pathological conditions most often seen are placenta previa, abruptio placentae, and the frequently overlooked rupture of the marginal sinus. Dr. Fish has organized an extremely comprehensive study of the problem.

Blood replacement is basic in the treatment of all three of these conditions. Facilities for the procurement of whole blood have been developed in most larger communities and arrangements for the establishment of an available supply in less populated areas is proposed.

The author clearly explains the anatomical aspects of placental hemorrhage. The clinical signs, symptoms, and diagnoses are considered. A most interesting and well-illustrated chapter is devoted to placental diagnosis. The concluding chapter outlines the author's theory of marginal sinus rupture. Case histories and an adequate bibliography are included.

Treatment, a most important feature, seemed in part archaic and necessitates a reserved recommendation of the monograph. Therapy with the Voorhees bags and uterine packs should have been included in and limited to the historical chapter.

**Pediatric Diagnosis.** By Morris Green and Julius Richmond. 436 pages. Philadelphia, 1954, W. B. Saunders Company. \$10.00.

The authors have included in a relatively small book most of the peculiarities which are associated with pediatric practice. In compiling such a mass of signs and symptoms

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\*The Advisory Committee on Policy has agreed that most book reviews need not be signed.

they, of necessity, had to be brief. It is the brevity of presentation and lack of illustrations which are the book's greatest shortcomings. The splendid descriptions of the psychological problems of pediatrics and the incorporation of references into the text proper are the best features of the book. One wonders whether a compendium such as this has any advantages over the standard pediatric textbooks now in use for teaching medical students and practitioners.

**Color Atlas of Pathology.** Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. 450 pages with 1,032 illustrations. Philadelphia, 1954, J. B. Lippincott Company. \$20.00.

This atlas of four hundred fifty pages is divided into five sections: disease of the endocrine system, gynecologic lesions and obstetric lesions, diseases of the breast, diseases of the male genital tract, and diseases of the skin. There are 1,032 figures in color on 343 plates. Each section has several pages of general discussion of the lesions in that particular section. Each color plate is usually composed of photomicrographs of actual case material with a short résumé of the case history.

The amount of material is tremendous and every lesion of the subjects covered is included. The time and effort necessary to have compiled the material must have been enormous. The different authors who took part in this undertaking are well-known authorities in their fields. One would thus expect an outstanding production. In spite of the wonderful histologic material, however, the final outcome is far from what one would anticipate. The reason is simple, namely, that in the photographing and printing most of the detail has been lost. Any illustration in a work of pathology should be clear enough to illustrate the point under discussion. Consequently, when this clarity is lost the value of the work is also lost.

The final product must be a disappointment to the authors who put so much time and effort into its development. This book may find a place on the shelves of medical students and general practitioners, but not in the hands of the discriminating pathologist.

**Diseases Affecting the Vulva.** By Elizabeth Hunt. 236 pages with 47 illustrations. St. Louis, 1954, The C. V. Mosby Company. \$9.00.

This fourth edition has been revised to bring the book up to date. Its two hundred twenty-seven pages may seem a great deal to be devoted to one area of gynecologic anatomy. It covers all conditions that may affect this area, however, and is easy reading. Since the author is a dermatologist, considerable space is devoted to dermatologic disturbances. In many respects, this is a valuable feature, for too frequently the gynecologist is ignorant of dermatology.

Considerable discussion is given to lichen planus, leukoplakic vulvitis, leukoplakia, and kraurosis. These lesions are not clearly described in most works dealing with gynecology, but in this book they are described in detail and the relationship to each other accurately defined. There could be some disagreement with the author's statements concerning the relationship of leukoplakia to carcinoma of the vulva, but if one uses the terms correctly the disagreement disappears.

The gynecologist will be disappointed in the small amount of space devoted to the discussion of carcinoma of the vulva.

The color plates are very good but the photomicrographs are not very informative.

**A Ciba Foundation Symposium on the Kidney.** Edited by A. A. G. Lewis and G. E. W. Wolstenholme. 333 pages with 125 illustrations. Boston, 1954, Little, Brown and Company. \$6.75.

Thirty-five participants from eight countries (twenty-two from Great Britain) took part in this international symposium on the kidney. There are twenty papers each followed by discussion. Some are rehashes, some present new data, some are speculative, and some clinical.



There are four papers in the first section on "Structural and Functional Relationships in the Kidney." Oliver reviewed some of his work on the study of isolated nephrons and Raaschou reported on renal biopsy findings. Darmady described anatomical changes found in the proximal convoluted tubules isolated from kidneys of patients with aminoaciduria. Wirz presented data suggesting that the loops of Henle may act as a counter-current system in which isosmotic urine entering the descending limb becomes hypertonic; as the urine goes up the ascending limb, it is again diluted to isotonicity. Blood obtained from venous capillaries near the hairpin turns is hypertonic to that in the cortex. Presumably the extracellular fluid in this region is also hypertonic and may serve to concentrate urine in the collecting tubules traversing this section.

In the section on "Tubular Functions Other Than the Regulation of Acid-base Balance," Bradley reported on variations in the "nephron population," as to the time spent in the tubules in formation of urine. About 60 per cent of the filtered molecules reach the bladder within 10 minutes, but 10 per cent require as long as 30 minutes. Taggart discussed the effect of acetate and other metabolic intermediates upon tubular excretion and speculated about enzyme systems possibly operative. Lambert presented some data on dextrose excretion in patients with tubular damage (poisons) and in renal diabetes. Reubi differentiated "true renal diabetes," characterized by low  $Tm_G$  (maximum tubular excretory capacity for glucose), from "renal pseudodiabetes" in which the dextrose titration curve is markedly splayed.

In the section on "Renal Share in the Regulation of Acid-base Balance," Robinson reviewed data which can be interpreted as pointing to the active reabsorption of sodium as the central process, with the excretion of acid, ammonia, and potassium as secondary effects. Pitts argued that the reabsorption of filtered bicarbonate-bound base depends in a large measure upon the plasma concentration and the carbon dioxide tension. In modification of his earlier view, he now thinks that such reabsorption may occur throughout the whole tubule. Berliner postulated that filtered potassium is reabsorbed high in the tubule and that urinary potassium is secreted further down the nephron. The latter process may be an exchange of potassium for sodium, with hydrogen ions competing with potassium in the exchange mechanism.

Sanderson found no evidence of renal damage induced by large amounts of sodium bicarbonate given to patients with gastric or duodenal ulcers.

Part four deals with "Mechanism of Sodium Retention." John Merrill reviewed some of the clinical conditions in which sodium retention occurs. In the discussion de Wardener presented a graph showing marked increases in chloride excretion induced by catheterization (in hypertensive patients; in normal patients the effect is slight). Le Quesne discussed postoperative retention of water and sodium; the former is primary and probably depends upon the pituitary antidiuretic hormone. There is a "primary" sodium retention, which appears on about the third postoperative day. Milne reported on electrolyte excretion (sodium, potassium, and bicarbonate) in mildly potassium-depleted subjects. Alwall discussed the treatment of acute uremia, especially with pulmonary edema, by dialysis on an artificial kidney. Dent presented some data on calcium and phosphate excretion as influenced by vitamin D, thyroxine, ammonium chloride, parathyroid hormone, and spontaneous diurnal variations. Borst attempted an explanation of diuresis in terms of three types: diurnal, water induced, and saline induced. The last is biphasic, the water being excreted first. Factors concerned in the regulation of extracellular volume include cardiac output in reference to "demand." Hamburger calculated the quantities of preformed and metabolic water arising from catabolism in patients with acute renal failure and in dogs with occluded ureters. The weight gains and the large volumes of water lost in the later diuresis were consistent with the calculations. He suggests that the cells are overhydrated while extracellular dehydration may exist in patients with acute renal failure. Black pointed up the gaps in knowledge as to how the kidney regulates the volume of extracellular fluid.

## Selected Abstracts\*

### Journal of the American Medical Association

*Vol. 154, March, 1954.*

Weinberg, A.: Radiological Estimation of Pelvic Expansion, p. 822.

Kaltreider, D. F.: The Contracted Outlet, p. 824.

*Vol. 154, April, 1954.*

\*Walsh, T. E.: The Effect of Pregnancy on the Deafness Due to Otosclerosis, p. 1407.

**Walsh: Effect of Pregnancy on Deafness Due to Otosclerosis, p. 1407.**

It is common belief in the medical profession that the deafness due to otosclerosis is made worse by pregnancy and that a woman with this disease should be advised against pregnancy, or advised to have a therapeutic abortion. The author reviewed the records of 243 women and added 40 of his own cases of women with fenestration operations for otosclerosis who have had one or more children since surgery. The author has followed his cases at yearly intervals by actual measurement, and has noticed no immediate postpregnancy loss of hearing. Dr. Walsh concludes that there is no evidence that pregnancy has a significant effect on deafness associated with otosclerosis, and that there seems to be no excuse for advising therapeutic abortion in women with otosclerosis.

DAVID P. BAUER, M.D.

*Vol. 155, June, 1954.*

Speert, H., and Guttmacher, A. F.: Frequency and Significance of Bleeding in Early Pregnancy, p. 712.

Wallace, H. M., Gold, E. M., Baumgartner, L., et al.: Trends in Maternal and Perinatal Mortality in New York City, p. 716.

Lilienfeld, A. M., and Posamanick, B.: Association of Maternal and Fetal Factors With the Development of Epilepsy, p. 719.

*Vol. 155, July, 1954.*

\*Livesay, W. R., Moyer, J. H., and Miller, S. I.: Treatment of Hypertension With Rauwolfia Serpentina Alone and Combined With Other Drugs, p. 1027.

Buxton, C. L., and Herman, W. L.: Effect of Thyroid Therapy on Menstrual Disorders and Sterility, p. 1035.

**Livesay, Moyer, and Miller: Treatment of Hypertension With Rauwolfia Serpentina Alone and Combined With Other Drugs, p. 1027.**

This report presents the results of treating hypertension of varying degrees of severity with Rauwiloid alone and with hydralazine or hexamethonium. A total of 84 cases of hypertensive vascular disease is included in this study. All patients were treated on an outpatient basis. The control blood pressure is the average of all blood pressures taken over at least a two-month period during which the patients received only placebo medications. Only patients with an average blood pressure greater than 150/100 mm. Hg were included in this study. The criterion for responsiveness was a reduction in blood pressure below 150/90 mm. Hg. When a second drug was added, a return to normotensive range was considered a response to combined therapy. Of the 43 patients treated with alseroxyton alone there were 20 patients who obtained a significant reduction in blood

\*Titles preceded by an asterisk are abstracted below.

pressure, from an average of 204/119 to 157/95 mm. Hg. The average pulse rate decreased from 86 to 70 beats per minute. The side effects were sedation, increased appetite and weight gain, and a sense of well-being. There was no improvement in the electrocardiogram, heart size, or fundi. Sixty per cent of patients with headaches showed improvement, 60 per cent of those with angina improved, and 18 per cent of those with heart failure improved. Of the 21 patients treated with alseroxylon and hydralazine combined, 12 showed a significant fall in blood pressure, from an average of 232/130 to 182/104 mm. Hg. The average control pulse rate was 87 beats per minute and with combined therapy it was 72 beats per minute. Twenty-five patients received hexamethonium alone and 22 of these patients were responsive, from an average of 208/130 to 154/104 mm. Hg. When alseroxylon was added, 15 patients showed further response and 13 became normotensive. Only two of eight patients with Grade 4 retinopathy failed to show improvement. As a result of this study, the authors outline a new approach to the treatment of hypertension using alseroxylon alone or combined with other hypotensive drugs.

DAVID P. BAUER, M.D.

*Vol. 156, September, 1954.*

Thoms, H., and Wiedenbach, E.: Support During Labor, p. 3.

### Deutsche medizinische Wochenschrift

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Buehlmann, A., Schaub, F., and Luchsinger, P.: Evaluation of Commissurotomy in Mitral Stenosis, p. 630.

*Vol. 79, Nos. 27/28, July 2, 1954.*

\*Mittelstrass, H.: Prophylactic Chemotherapy in Obstetrics, p. 1078.

**Mittelstrass: Prophylactic Chemotherapy in Obstetrics, p. 1078.**

The author feels that chemotherapy should not be used promiscuously. It is his opinion, however, that the incidence of puerperal sepsis can be decreased considerably by the use of a combination of sulfonamides and penicillin. The suggested indications are: any intrauterine manipulation, prolonged labor, ruptured membranes for over 24 hours, in addition to obvious infection.

WALTER F. TAUBER, M.D.

*Vol. 79, Nos. 29/30, July 16, 1954.*

Lauffs, E.: Sclerosing of Vulvar Varicosities, p. 1134.

*Vol. 79, Nos. 31/32, July 30, 1954.*

\*Kirchhoff, H.: The Influence of Sociological Factors on the Cause and Cure of Gynecological Carcinoma, p. 1153.

Bechmann, R., Feldmann, F., and Schuemmelfeder, N.: Problems of Erythroblastosis Fetalis, p. 1157.

Halfpap, E.: Contribution on the "Perinatal" Mortality of Infants, p. 1172.

Martius, G.: The Perinatal Care of Premature Infants by the Obstetrician, p. 1188.

**Kirchhoff: Influence of Sociological Factors on Cause and Cure of Gynecological Carcinoma, p. 1153.**

The author reviews the previous literature in which it is indicated that economic circumstances affect the development and clinical course of gynecological cancers. Those in the higher economic strata are more susceptible to adenocarcinoma of the corpus, while poorer women have a much higher incidence of epidermoid carcinoma of the cervix. In either type, virulence seems to be greater in the poor. The present study confirms previous impressions. There is a 20 to 25 per cent difference in the five-year survival rate for all types. This appears to be statistically significant despite the admitted weakness in any such classification. The obvious conclusion is drawn that therapy must not be limited to purely surgical and/or radiological measures, but must, as far as possible, include environmental control.

WALTER F. TAUBER, M.D.

*Vol. 79, No. 39, Sept. 24, 1954.*

\*Frangenheim, H.: The Influence of Cesarean Sections on Subsequent Deliveries, p. 1451.

**Frangenheim: Influence of Cesarean Sections on Subsequent Deliveries, p. 1451.**

The author allows about 60 per cent of patients with previous cesarean sections to deliver vaginally. In 422 cases reported, he has an incidence of 9 ruptures through the old scar, 8 of which were in longitudinal uterine incisions. The incidence of corrected fetal mortality in his series is 2.9 per cent. He reports no maternal mortality. It is his conclusion that the following factors contribute to safe vaginal delivery in patients with previous sections: (1) hospitalization for delivery, (2) careful history to determine indica-



tion for previous section, (2) adequate sedation and avoidance of oxytocics, (4) readiness to perform section immediately if indicated, (5) proper surgical technique at first section including transverse, low cervical uterine incision; proper closure of uterine wound; and postoperative care to avoid infection.

WALTER F. TAUBER, M.D.

*Vol. 79, No. 40, Oct. 1, 1954.*

Naujoks, H.: Malpractice Suit Arising Out of a Case of Spontaneous Delivery With "Birth Trauma," p. 1478.

*Vol. 79, No. 41, Oct. 8, 1954.*

Martius, H.: Twenty-eight Years of Obstetrics and Gynecology, p. 1505.

\*Mohr, H.: Clinical Investigation of Increased Lactation, p. 1513.

Seitz, L.: On the Problems of Eclampsia, p. 1518.

Philippe, E., and Stange, H.: The Polycystic Ovary (Stein-Leventhal Syndrome), p. 1519.

Naujoks, H.: Do Obstetrical Operations Require the Husband's Consent? p. 1536.

**Mohr: Clinical Investigation of Increased Lactation, p. 1513.**

Controlled experiments are presented, indicating that Alyt, an extract of the shrub *Agnus castus*, increases the milk production without affecting the composition of the mother's milk. Side effects noted are: (1) urticaria, treated readily with antibiotics and topical antipruritic agents; (2) early re-establishment of menses.

Pharmacologically, it appears that the extract acts through the pituitary.

WALTER F. TAUBER, M.D.

### Wiener klinische Wochenschrift

*Vol. 66, No. 12, March 26, 1954.*

Froewis, J.: Tuberculosis of the Female Genital Tract, p. 201.

*Vol. 66, No. 14, April 9, 1954.*

\*Rauscher, H.: The Importance of the Ovum in Failure to Conceive, p. 242.

**Rauscher: Importance of Ovum in Failure to Conceive, p. 242.**

The author reviews briefly the manifold causes of infertility. After organic causes in both marital partners have been ruled out, the diagnosis of sterility must be deferred until it has been carefully ascertained that the following rules have been observed: (1) continence to avoid oligospermia; (2) coitus just at the time of ovulation as determined by daily cervical smears. This must be done for many months. Ovulation time can be determined almost to the hour from cervical smears. If, despite these precautions, pregnancy does not supervene, defective ova may be at fault. The author has histological proof for this. Since the eggs are not identical from cycle to cycle, this regimen may have to be continued for many months.

WALTER F. TAUBER, M.D.

*Vol. 66, No. 15, April 16, 1954.*

Homma, H.: The Diagnosis of Ectopic Pregnancy From Uterine Curettings, p. 265.

*Vol. 66, No. 20, May 21, 1954.*

\*Gitsch, E.: The Treatment of Menopausal Syndrome With Adenine Compounds With Particular Consideration of Gonadotropin Excretion, p. 354.

**Gitsch: Treatment of Menopausal Syndrome With Adenine Compounds With Particular Consideration of Gonadotropin Excretion, p. 354.**

The author has treated 70 menopausal women with severe symptoms, using nuclear material from the exocrine portion of the pancreas with good results in reducing such symptoms as flushes.

There were no untoward side effects. While it appears that there is some influence on the pituitary, this is by no means considered proved.

WALTER F. TAUBER, M.D.

*Vol. 66, No. 22, June 4, 1954.*

\*Froewis, J., Kremer, H., and Narik, G.: Indications for and Results of the Watkins' Interposition Operation, p. 391.

**Froewis: Indications for and Results of Watkins Interposition Operation, p. 391.**

The authors consider the Watkins interposition operation as best for cystocele, prolapse of the uterus, and stress incontinence. In their hands, the following results were obtained: 75 per cent cure and 20 per cent improvement of incontinence and 70 per cent cure and 15 per cent improvement of various types of prolapse. This compares favorably with the results obtained with other operations for these conditions. They advise that great care be taken in positioning the uterus properly and that small or atrophic uteri be fixed to the pubic rami to avoid recurrence. Good posterior colporrhaphy is also required.

WALTER F. TAUBER, M.D.

*Vol. 66, No. 31, Aug. 6, 1954.*

Brandl, K., and Pieha, E.: Examination and Treatment of Vaginitis, p. 546.

*Vol. 66, No. 33, Aug. 20, 1954.*

\*Burkl, W.: The Interstitial Cells of the Gonads as the Site of Sex Hormone Production, p. 575.

**Burkl: Interstitial Cells of Gonads as Site of Sex Hormone Production, p. 575.**

It is demonstrated by a new histochemical method that Leydig cells in the testis and stromal cells in the ovary produce testosterone and estrogen, respectively.

WALTER F. TAUBER, M.D.

*Vol. 66, No. 34, Aug. 27, 1954.*

Hofstaetter, R.: The Usefulness of Wessely's "Relascope" in the Early Diagnosis of Uterine Cancer, p. 590.

### Journal of the National Cancer Institute

*Vol. 14, No. 5, April, 1954.*

\*Waltz, Helen K., Tullner, William W., Evans, Virginia J., Hertz, Roy, and Earle, Wilton R.: Gonadotrophic Hormone Secretion From Hydatid Mole Grown in Tissue Culture, p. 1173.

**Waltz, Tullner, Evans, Hertz, and Earle: Gonadotrophic Hormone Secretion From Hydatid Mole Grown in Tissue Culture, p. 1173.**

The authors obtained fresh surgical specimens from four cases of hydatid mole. The vesicles were cut into small sections. Tissue pieces of comparable weight from the same bleb were paired; one piece was frozen for assay and the other was planted. The culture fluid was composed of: 20 per cent chick-embryo extract, 40 per cent horse serum, and 40 per cent Earle's saline containing penicillin and streptomycin. A modified Levin-Tyndale test was employed in doing the biological assays.

The studies revealed that the heterologous cultures produced gonadotrophic hormone over an extended period of time—as long as 413 days in one case. In addition, increases in gonadotrophic activity from 600 to 15,000 per cent were demonstrated. Not only were the authors unable to predict the gonadotrophic activity of the mole from the potency of the original tissue homogenate, but, also, study of cell types in the living culture did not indicate any particular cell type as the source of the gonadotrophic hormone.

JOHN G. MASTERSON, M.D.

**Irish Journal of Medical Science**

*Vol. (Series) 6, No. 340, April, 1954.*

\*Drury, M. I.: Anaemia in Pregnancy, p. 172.

\*Dunton, Sheamus: Haemolytic Disease of the Newly-Born, p. 177.

O'Flynn, J. Dermot: A Case of Renal Failure: Response to Treatment With Hypertonic Glucose Given Through an Intracardiac Catheter, p. 180.

**Drury: Anaemia in Pregnancy, p. 172.**

The author makes a plea for the prevention of iron-deficiency anemia in pregnancy but states, "It is unfortunate that it is to a large extent outside the province of the doctor." He points out the necessity for better housing, better feeding, and better education by simple instruction in cooking. The author gives the impression that the high stillbirth and "infantile mortality rates" are a reflection of the prevalence of anemia in his country.

The great proportion of this communication is directed toward a consideration of megaloblastic anemia of pregnancy and the puerperium. The author discusses the etiology and treatment of this condition, as well as the clinical features. He claims that the classic indices may be of no value in making the diagnosis because of the presence of a microcytic peripheral blood picture. It is pointed out that vitamin B<sub>12</sub> and refined liver are not the therapeutic agents of choice, but rather folic acid, crude liver, and proteolyzed liver. The author closes the presentation with three case reports.

SCHUYLER G. KOHL, M.D.

**Dunton: Haemolytic Disease of the Newly-Born, p. 177.**

In this presentation on treatment of hemolytic disease in infants of Rh-negative sensitized mothers, the thesis of the author is that "since many of these infants are still-born if allowed to proceed to term it would appear to be a logical maneuver to induce premature birth of the infant." The author acknowledges that this thesis is not uniformly held and therefore he presents 50 cases treated by induction of labor followed by exchange transfusion. In his series, the inductions were carried out between the thirty-third and thirty-eighth weeks. Labor was induced by the following methods: medical induction, bougie induction, and rupture of the membranes.

In the series of 50 patients so treated, there were no stillbirths and there were 8 neonatal deaths. Each infant was treated by exchange transfusion. It was necessary to repeat exchange transfusions in 5 cases and subsequent simple blood transfusion in 17 cases. These 50 pregnancies occurred in women who had previously had 190 pregnancies. The previous pregnancies had resulted in 112 surviving children, 36 stillbirths, and 42 neonatal deaths. This gave a previous fetal loss of 41 per cent. The present group had a 16 per cent fetal loss. The difference between these two percentages of fetal loss is statistically significant.

SCHUYLER G. KOHL, M.D.

*Vol. (Series) 6, No. 343, July, 1954.*

\*Lillie, E. W., Gatenby, P. B. B., and Moore, H. C.: A Survey of Anaemia in 4,314 Cases of Pregnancy, p. 304.

Collis, W. R. F.: The Trend of Medical Education in Ireland, p. 313.

**Lillie, Gatenby, and Moore: Survey of Anaemia in 4,314 Cases of Pregnancy, p. 304.**

Anemia is a major complication of pregnancy in Ireland. The current report is from the Rotunda Hospital and covers their experience for the year 1953. The incidence of anemia (less than 10 Gm. hemoglobin) was 23.8 per cent. Among these women there were a few cases of megaloblastic anemia and an occasional case of hemolytic anemia. The author lists and discusses diagnostic methods, signs, and symptoms, the differential diagnosis, and suggestions for treatment. There is also a short discussion of etiology.

SCHUYLER G. KOHL, M.D.

**American Journal of Medical Science***Vol. 228, August, 1954.*

\*Finnerty, Frank A., Jr.: The Use of 1-Eydrazinophthalazine (Apresoline) in the Management of Hypertension Appearing Early in Pregnancy, p. 140.

**Finnerty: Use of 1-Hydrazinophthalazine (Apresoline) in Management of Hypertension Appearing Early in Pregnancy, p. 140.**

Oral 1-hydrazinophthalazine in doses of 200 to 300 mg. per day was given as the sole therapeutic agent to 91 pregnant women with hypertension. All women were followed for at least three weeks and the average duration of therapy was 6.5 weeks.

Forty per cent responded with drops of at least 20 mm. Hg in the diastolic blood pressure, disappearance of symptoms, and a decrease in edema and proteinuria. Substitution of a placebo was followed by relapse. Half of the patients treated gave a poor-to-fair response. The proportions of patients who responded favorably was about the same in the 3 groups studied—those with essential hypertension, those with pre-eclampsia, and the 2 concurrently.

LEON C. CHESLEY, PH.D.

**Canadian Medical Association Journal***Vol. 71, No. 2, August, 1954.*

Quick, D.: The Influence of Radium on Cancer Therapy, p. 103.

Gold, Solomon: High Calcium Intake in the Last Month of Pregnancy, p. 166.

*Vol. 71, No. 3, September, 1954.*

Lyons, B. H., and Lyons, R.: Coronary Artery Disease in Pregnancy, p. 267.

*Vol. 71, No. 4, October, 1954.*

MacKenzie, D. A., and Janes, J. M.: Postmenopausal Osteoporosis: A Programme of Treatment in 42 Cases, p. 339.

\*MacKinnon, K. J., and Smith, E. C.: Vesical Neck Obstruction in Women, p. 356.

Robinson, S. C.: Obstetrics in Rural Practice, p. 372.

**MacKinnon and Smith: Vesical Neck Obstruction in Women, p. 356.**

Obstruction of the neck of the female bladder is less common than inflammatory lesions of the bladder neck and urethra, but occurs often enough to warrant a careful search for it. The symptoms are troublesome but not diagnostic. The treatment is resection of the vesical neck. Infection is the most common cause for this disturbance and urinary frequency the commonest symptom. The disturbance rarely occurs prior to the age of 30.

Cystograms should be taken in suspected cases and intravenous pyelography performed in all cases.

The treatment of choice is a transurethral resection of the vesical neck through a McCarthy resectoscope. Care must be taken not to remove too much tissue.

The author reports 12 cases with cure of symptoms in 7, 3 greatly improved, one cured by a repeat resection, and one death from coronary occlusion three months after operation.

J. EDWARD HALL, M.D.



## Correspondence

### Interpretation of Pelvimetric Films—Whose Responsibility?

*To the Editors:*

An article in the August, 1954, JOURNAL, by Walsh, Haas, and Maclean of Washington, D. C., has recently come to my attention. I think it a very excellent article and I agree with their findings in every respect with the exception of their statement in the summary that "It cannot be too strongly emphasized that an obstetrician should be responsible for mensuration and interpretation of the films."

This statement has been made by other obstetricians and it seems to me that it is just as wise for the radiologist to be arrogant about his findings and say the matter belongs in his hands. It is just as easy for a radiologist to be able to appreciate the problems of the obstetrician as it is for the obstetrician to appreciate the problems of the radiologist.

What these authors say is perfectly true, provided the radiologist has not taken the time to consult with his obstetric confrere. To quote from an article I<sup>1</sup> wrote not long ago, I think this should be our attitude: "The roentgenologist's interpretation of the obstetric pelvis will have limited value if his knowledge of the physiologic mechanism and pathology of labor is not adequate. A clinical appreciation is necessary for all forms of roentgen diagnosis, but particularly in the case of pelviography and cephalography. There may be some radiologists not well grounded or interested enough in the obstetric aspect of radiology to be good consultants.

"We disagree with the obstetricians to this extent, however, that under certain circumstances there is actually a need for a good radiologic consultant. Even though ideally the interpretation belongs in the hands of the obstetrician in the majority of cases, there may be other instances where there is no other possible means of adequate interpretation.

"We have always warned that the obstetrician should be in constant consultation with the radiologist and that the radiologist must not render a clinical prognosis unless he is in consultation with the obstetrician. He should be fairly objective in his findings; otherwise, he will entirely mislead rather than help. He does, nevertheless, have one very important function, i.e., that of keeping the clinician from reading things into the x-ray findings. As is necessary in all other procedures of radiology, he stands watch to prevent exploitation of the x-ray findings. In the small clinic or in private practice, one must be concerned about the obstetrician who may not be too scrupulous and who may refer a case to the radiologist purely for reasons of justifying operative procedure. This the radiologist can forestall. He can prevent wishful thinking which may influence the obstetrician's report in this respect, and thus prevent unnecessary cesarean section.

"In a large institution where it is possible for the radiologist to surrender the job of interpretation entirely to the obstetrician, the situation will be quite different, but there will still be times when the radiologist will actually know more than the referring obstetrician. He will have to take over the job of a teacher, if for no other reason than to try to correct the mistaken general impression that the x-ray examination is a panacea."

PAUL C. SWENSON, M.D.

JEFFERSON MEDICAL COLLEGE OF PHILADELPHIA  
PHILADELPHIA, PA.  
FEB. 10, 1955

### Reference

1. Swenson, P. C., Goldberger, A., and O'Neill, H. A.: Southwest. Med. 31: 152, 1950.

**Reply by Dr. Walsh**

*To the Editors:*

I was gratified to read Dr. Paul Swenson's comments and am not at all surprised that he objected to our statement, "It cannot be too strongly emphasized that an obstetrician should be responsible for mensuration and interpretation of the films." It was pleasing to me to have Dr. Swenson approve the remainder of the context of the paper. He has displayed an unusual degree of interest in pioneering x-ray pelvimetry as we know it today. He was associated with Drs. Caldwell and Moloy for several years and I am sure that a considerable amount of good obstetrics was absorbed by Dr. Swenson as a result of this association, just as Drs. Caldwell and Moloy must have benefited from their association with him. How many radiologists have enjoyed such fine obstetrical association? How many radiologists have Dr. Swenson's keen interest in the subject?

I agree with Dr. Swenson's quotation from his article on "Practical Obstetric Roentgenography." We are happy to know that we can call on our radiologists for consultation over doubtful and difficult films. We frequently call upon these gentlemen who graciously allow us of the obstetrical service to be responsible for the interpretation of pelvimetric studies. In our clinic, we try to teach the radiology resident staff, as well as our own, the fundamentals of x-ray pelvimetry.

We feel that the question raised by Dr. Swenson resolves itself to point of view. Whose point of view? The radiologist quite righteously feels that the obstetrician is invading his field when he prefers to read his own films. We, as obstetricians, would prefer to measure and interpret our own films and feel that every obstetrician should be capable of doing so. After all, the ultimate decision in the management of an obstetrical problem should rest with the obstetrician.

Actually we are not far apart in thought. Even though I have not changed my opinion, we are agreed that frequent and close consultation and cooperation between the obstetrician and radiologist will bring out the best in interpretation of films taken of the obstetric patient.

JOHN W. WALSH, M.D.

2023 R STREET, N.W.  
WASHINGTON 9, D. C.  
MARCH 9, 1955

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**Progesterone Therapy in Threatened Abortion**

*To the Editors:*

The February, 1955, JOURNAL contains an article by Baker and associates, entitled "The Value of Urinary Pregnanediol Determinations as an Indication for the Use of Progesterone in the Treatment of Threatened Abortion," which I wish to discuss. First, the authors misquote Guterman and Tulsky as having "reported favorably on progesterone when used in large doses in treating threatened abortion." What we were very careful to say was that large doses *might* be of value in that group of patients with threatened abortion and a persistently low pregnanediol excretion. It is the downward trend in excretion which might justify progesterone administration. This same point was re-emphasized by Koff and Tulsky<sup>1</sup> in a subsequent article on threatened abortion. This should not be construed as advocating large doses of progesterone in all cases of threatened abortion.

Second, it should be noted that the majority of the authors' cases fall in the second trimester of pregnancy (late abortion). There is much evidence that the factors responsible for early abortion may be different from those causing late abortion, and because organic factors are so frequently operative in the latter group, pregnanediol assays have been found to be of little or no value there. For this reason, most studies of the endocrine aspects of abortion have been restricted to the first trimester.

Third, despite the gradual rise in pregnanediol excretion as pregnancy advances, marked daily variations occur, especially beyond the twelfth week, which vitiate the importance of a solitary reading. Although these variations are not as noticeable in the first ninety days, one cannot consider an isolated reading as being indicative of the health of the pregnancy. By the same token, one cannot accept isolated readings more than 48 hours apart as an indication of the level of pregnanediol excretion.

Fourth, I wish to point out that because of the diurnal variations in pregnanediol excretion, one cannot say that a 12 hour specimen of urine contains 50 per cent of the 24 hour output—it may be much more or less. It was for this reason that we discontinued the use of the 12 hour specimen shortly after the beginning of our study some years ago. It could not be considered to reflect accurately the hormonal level of the patient. I suspect that if the authors repeat their study on patients with threatened abortion in the first trimester of pregnancy only, and utilize daily 24 hour urine specimens for pregnanediol analysis for at least three days, they will find that 95 per cent or more of their patients with consistently low pregnanediol values will abort.

As a result of these various considerations, I find that I can agree only with the last of the authors' conclusions "that progesterone therapy is not indicated in patients with a normal excretion of pregnanediol in the 24 hour urine and is of doubtful value where the urinary pregnanediol level is found to be subnormal."

ALEX S. TULSKY, M.D.

MICHAEL REESE HOSPITAL  
CHICAGO, ILLINOIS  
MARCH 11, 1955

### Reference

1. Koff, A., and Tulsy, A. S.: S. Clin. North America 33: Feb., 1953.

### Reply by Commander Baker

*To the Editors:*

We referred to the work of Guterman and Tulsy (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 58: 495, September, 1949) and it was not our intention to misconstrue in any manner the context of the article as written by them. If the authors did not wish to infer that the administration of much larger doses of progesterone in their series of cases would have resulted in a better salvage by replacing the physiological requirements of the host and thus resulting in a smaller number of abortions than noted in their series, then we have misinterpreted their work and offer our sincere apologies. However, the objection raised by Dr. Tulsy to our cases being made up of mostly second trimester abortions is not pertinent. According to Swyer<sup>1</sup> and De Watteville,<sup>2</sup> the pregnanediol output is quite constant and can be used for detection of progesterone deficiency at any stage of gestation after four weeks until term. It is certainly true there will be daily variations in the values of excreted pregnanediol and this fact only emphasizes that multiple determinations are undoubtedly to be preferred but unfortunately this is not always practical from the standpoint of the clinician. We admit that 12 hour urine specimens probably do not contain actually 50 per cent of the excreted pregnanediol due to the variations already discussed by Dr. Tulsy but when doubled did approximate closely enough for practical purposes the 24 hour urine excretion of pregnanediol and could be utilized as a guide to therapy.

Another factor is the extremely high incidence of developmental and degenerative defects of the ovum and trophoblast reported by certain investigators<sup>3, 4</sup> as the cause of abortion. Dr. Tulsy in his paper admitted there was no investigation made of the abortuses in their series. We feel, if this had been carried out, the abortuses of the 40 patients with normal pregnanediol levels, 16 of whom had been given progesterone,

probably would have been found to be defective and the urinary pregnanediol level would have been of no benefit in determining prognosis in any case as noted in Conclusion Ten in our own study.

The urinary pregnanediol excretion level is reportedly representative of the major metabolic breakdown product of progesterone by the host and is supposedly fairly constant in its production during pregnancy any time after four weeks until term, and should be a measurable substance in the second trimester as well as the first. If this is not so, as inferred by Dr. Tulsy, then we must discount the practical value of the Guterman test as a means of determining the prognosis in so-called late abortions and restrict its use entirely to those occurring in the first twelve weeks of gestation.

W. S. BAKER, JR., COMMANDER (MC) USN

U. S. NAVAL HOSPITAL  
SAN DIEGO 34, CALIFORNIA  
MARCH 22, 1955

### References

1. Swyer, G. I. M.: Brit. M. J. 1: 619, 1952.
2. De Watteville, H.: J. Clin. Endocrinol. 11: 251, 1951.
3. Wall, R. L., and Hertig, A. T.: AM. J. OBST. & GYNEC. 56: 1127, 1948.
4. Colvin, E. D., Bartholomew, R. A., Grimes, W. H., and Fish, J. S.: AM. J. OBST. & GYNEC. 59: 1208, 1950.

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### Items

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#### **Sixteenth Congress of La Société de gynécologie et d'obstétrique de la langue française**

The Sixteenth Congress of the Société de gynécologie et d'obstétrique de la langue française will hold its annual meeting in Brussels from Sept. 22 to 26, 1955.

Notification of intention to attend should be sent to R. Vokaer, Le Secrétaire Général, 309 Avenue Molière, Bruxelles.



## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January and July)

- American Academy of Obstetrics and Gynecology.** (1945) *President*, William F. Mengert. *Secretary*, C. Paul Hodgkinson, 17546 Meadowood Ave., Lathrup Village, Birmingham, Mich.
- American Gynecological Society.** (1876) *President*, Isidor Clinton Rubin. *Secretary*, John I. Brewer, 104 S. Michigan Ave., Chicago 3, Ill. Next meeting, The Shoreham, Washington, D. C., May 21-23, 1956.
- American Association of Obstetricians and Gynecologists.** (1888) *President*, Thaddeus L. Montgomery. *Secretary*, Frank R. Lock, Bowman Gray School of Medicine, Winston-Salem, N. C. Annual meeting at Hot Springs, Va., Sept. 8, 9, and 10, 1955.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Frank L. McPhail. *Secretary*, Edwin J. DeCosta, 104 S. Michigan Ave., Chicago 3, Ill. Annual meeting at Columbus, Ohio, Oct. 6, 7, and 8, 1955; New Orleans, La., Oct. 4, 5, and 6, 1956.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, Waverly R. Payne. *Secretary*, Charles H. Mauzy, Bowman Gray School of Medicine, Winston-Salem, N. C. Next meeting, Hollywood Beach Hotel, Hollywood Beach, Fla., Jan. 28-Feb. 1, 1956.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Frederick H. Falls, *Secretary*, D. Frank Kaltreider, University Hospital, Baltimore 1, Md. Meetings with annual A.M.A. meetings.
- Society of Obstetricians and Gynaecologists of Canada.** (1944) *President*, A. M. Agnew, Vancouver, B. C. *Secretary*, F. P. McInnis, 1230 Avenue Road, Toronto, Ont. Next meeting, Bigwin Inn, Muskoka, Ont., June 17, 18, and 19, 1955.
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- Akron Obstetrical and Gynecological Society.** (1946) *President*, Edward F. Hellwig. *Secretary*, Carl J. Paternite, 159 S. Main St., Akron, O. Meetings, quarterly.
- Alabama Association of Obstetricians and Gynecologists.** (1940) *President*, Joe W. Perry. *Secretary*, James H. French, 927 Bell Bldg., Montgomery.
- Alameda County Gynecological Society.** (1951) *President*, Victor Koerper. *Secretary*, Wallace Lawson, 2975 Telegraph Ave., Berkeley, Calif. Meetings, fourth Wednesday of each month except June, July, August, and December.
- Arkansas Obstetrical and Gynecological Society.** (1953) *President*, Charles R. Wickard, Little Rock. *Secretary*, J. F. Kelsey, Fort Smith. Meetings, spring and fall.
- Atlanta Obstetrical and Gynecological Society.** (1954) *President*, R. A. Bartholomew. *Secretary*, George A. Williams, Suite 6, 710 Peachtree St., N. E., Atlanta 5, Ga. Meetings quarterly.
- Birmingham Obstetrical and Gynecological Society.** (1949) *President*, Hunter Brown. *Secretary*, Clay Wells, 1908 8th Ave., South, Birmingham, Ala. Four meetings annually.
- Boston, Obstetrical Society of.** (1861) *President*, Duncan E. Reid. *Secretary*, A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, third Tuesday of October, November, January, February, and March.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Alex Charlton. *Secretary*, John S. Giaccone, 1488 Metropolitan Ave., Bronx 62, N. Y. Meetings, fourth Monday, October through April, inclusive.
- Brooklyn Gynecological Society.** (1890) *President*, William Levine. *Secretary*, Leslie H. Tisdall, 615 Third St., Brooklyn 15. Meetings, third Wednesday, October, November, January, February, March, April, and May.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, Robert C. McDowell. *Secretary*, Louis A. Trippe, 511 Lafayette Ave., Buffalo 22, N. Y. Meetings, first Tuesday, October through May.

\*Changes, omissions, and corrections should be sent to the publisher, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

- Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Charles Gwynn. *Secretary*, William Redfield, 1502 State Tower Bldg., Syracuse 2. Meetings, second Tuesday, January, March, May, September, and November.
- Chicago Gynecological Society.** (1878) *President*, J. P. Greenhill. *Secretary*, Clyde J. Geiger, 4753 Broadway, Chicago 40. Meetings, third Friday, October through June.
- Cincinnati Obstetrical Society.** (1876) *President*, Richard D. Bryant. *Secretary*, John F. Mohan, 3731 St. Lawrence, Cincinnati 5. Meetings, third Thursday, September through May.
- Cleveland Society of Obstetrics and Gynecology.** (1947) *President*, O. B. Pomeroy. *Secretary*, Eduard Eichner, 10605 Chester Ave., Cleveland 6. Meetings, fourth Monday, September, November, January, March, and May.
- Columbus Obstetric-Gynecologic Society.** (1944) *President*, Anthony Ruppertsberg, Jr. *Secretary*, Fred B. Hapke, 350 E. Broad St., Columbus 15, Ohio. Meetings, last Wednesday of month, September through May.
- Dallas-Fort Worth Obstetrical and Gynecological Society.** (1948) *President*, Hugh Savage. *Secretary*, H. I. Kantor, 3534 Maple Ave., Dallas. Meetings, spring and fall.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, E. Stewart Taylor. *Secretary*, Charles R. Freed, 1809 E. 18th Ave., Denver 18, Colo. Meetings, first Monday of every month, October through May, inclusive, unless otherwise notified.
- El Paso County Obstetrical and Gynecological Society.** (1948) *President*, Erich Spier. *Secretary*, Alvin L. Perry, 209 Medical Arts Bldg., El Paso, Texas. Meetings, last Thursday, every other month.
- Florida Obstetric and Gynecologic Society.** (1948) *President*, J. Champneys Taylor. *Secretary*, R. B. Chrisman, Jr., 701 duPont Bldg., Miami 32. Meetings, December and April.
- Georgia State Obstetrical and Gynecological Society.** (1951) *President*, Albert J. Kelly. *Secretary*, Eugene L. Griffin, 26 Linden Ave., N. E., Atlanta. Next meeting, Augusta, May 1-4, 1955.
- Harris, John Warton, Obstetrical Society.** (1953) *President*, E. Russell Muntz. *Secretary*, Alice D. Watts, 324 E. Wisconsin Ave., Milwaukee 2, Wis. Meeting, Sept. 2 and 3, 1955.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, James T. S. Wong. *Secretary*, Fugate Carty, Straub Clinic, Thomas Square, Honolulu. Meetings, third Monday of each month at the Mabel Smythe Memorial Bldg.
- Houston Obstetrical and Gynecological Society.** (1939) *President*, M. J. Meynier, Jr. *Secretary*, Thomas G. Gready, Jr., 608 Hermann Professional Bldg., Houston. Meetings, first Tuesday each month, October through June.
- Indianapolis Obstetrical and Gynecological Society.** (1947) *President*, Carl P. Huber. *Secretary*, John F. Spahr, Jr., Suite 902, 23 East Ohio St., Indianapolis 4. Meetings, second Wednesday in January, April, and October.
- Interurban Obstetrical and Gynecological Society.** (1949) *President*, Fred Fumia, Rochester, N. Y. *Secretary*, E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y. Meeting, Hotel Seneca, Rochester, Oct. 8, 1955.
- Iowa Obstetrical and Gynecological Society.** *President*, L. G. Carrigg, Cedar Rapids. *Secretary*, William C. Keettel, State University of Iowa Hospitals, Iowa City. Meetings, spring and fall.
- Kansas City Gynecological Society.** (1922) *President*, Leroy A. Calkins. *Secretary*, James E. Keeler, 4301 Main St., Kansas City, Mo. Meetings, third Thursday, September, November, January, and March, and first Thursday in May.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, A. B. Barrett, Lexington. *Secretary*, R. C. Bateman, 432 W. Main St., Danville. Annual meeting, spring, 1956.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Samuel Martins. *Secretary*, Walter C. Rogers, 39 Congress St., Pasadena 2, Calif. Meetings, second Tuesday, September, November, January, March, and May.
- Louisville Obstetrical and Gynecological Society.** *President*, William E. Oldham. *Secretary*, V. E. Masters, 517 Fincastle Bldg., Louisville 2. Meetings, fourth Monday, September, October, November, January, February, March, April, and May.
- Madison Obstetrical and Gynecological Society.** (1950) *President and Secretary*, Lee B. Stevenson, 16 S. Henry St., Madison 3, Wis. Meetings, first Tuesday each month except July and August.
- Maryland, Obstetrical and Gynecological Society of.** (1929) *President*, Everett S. Diggs. *Secretary*, Harry M. Beck, 700 N. Charles St., Baltimore 1. Meetings, second Thursday, October, December, February, and May.
- Memphis Obstetrical and Gynecological Society.** (1950) *President*, H. E. Atherton. *Secretary*, William F. Mackey, 1374 Madison Ave., Memphis, Tenn. Meetings, second Tuesday, November, January, March, and May.

- Miami Obstetrical and Gynecological Society.** (1946) *President*, Richard F. Stover. *Secretary*, Richard C. Forman, 427 Biltmore Way, Coral Gables, Fla. Meetings, second Thursday, January, March, May, and November.
- Michigan Society of Obstetricians and Gynecologists.** (1924) *President*, Harold A. Ott. *Secretary*, E. Bruce Foster, 853 Fisher Bldg., Detroit 2. Meetings, first Tuesday, October, November, December, February, March, April, and May.
- Milwaukee Gynecological Society.** (1951) *President*, F. J. Hofmeister. *Secretary*, L. T. Servis, 425 East Wisconsin Ave., Milwaukee 2, Wis. Meetings, last Monday, January, March, May, and November.
- Minnesota Obstetrical and Gynecological Society.** *President*, Leonard A. Lang, Minneapolis. *Secretary*, Edward A. Banner, 200 First St., Southwest, Rochester, Minn. Meetings, spring and fall.
- Mississippi Obstetrical and Gynecological Society.** (1947) *President*, Claude G. Callender, Jackson. *Secretary*, J. A. K. Birchett, Jr., The Street Clinic, Vicksburg. Meetings May and October.
- Mobile County Obstetrical and Gynecological Society.** (1949) *President*, H. B. Dowling. *Secretary*, J. R. Mighell, 1302 Government St., Mobile, Ala. Meetings, quarterly when called.
- Montgomery County (Ohio) Obstetrical and Gynecological Society.** (1937) *President*, L. O. Fredericks. *Secretary*, A. A. Kunnen, 406 Harries Bldg., Dayton, Ohio. Meetings, third Wednesday of each month.
- Montana Obstetrical and Gynecological Society.** (1946) *President*, David Gregory. *Secretary*, Frank Pickett, Bozeman.
- Nassau Obstetrical Society.** (1944) *President*, Richard L. Jones. *Secretary*, George E. Christmann, 1502 Mott Avenue, Far Rockaway, N. Y. Meetings, second Monday, October, December, February, and April.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Lewis P. James. *Secretary*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings, spring and fall.
- New Haven Obstetrical and Gynecological Society.** (1946) *President*, Harry Conte. *Secretary*, Fred Gibson, 37 Trumbull St., New Haven, Conn. Meetings, third Tuesday, September, November, March, and May.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Benjamin Devers. *Secretary*, Paul Grossbard, 162 Lexington Ave., Passaic. Meetings, October and April.
- New Mexico Obstetrical and Gynecological Society.** (1947) *President*, M. D. Bivens. *Secretary*, J. W. Wiggins, 24 Medical Arts Square, Albuquerque. Meetings, quarterly.
- New Orleans Gynecological and Obstetrical Society.** (1924) *President*, John C. Weed. *Secretary*, Abe Mickal, 1413 Richards Bldg., New Orleans. Meetings, October, November, January, March, and May.
- New York Obstetrical Society.** (1863) *President*, Morris A. Goldberger. *Secretary*, George L. Bowen, 101 East 74th St., New York. Meetings, second Tuesday, October through May.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Adam Thorp. *Secretary*, Fleming Fuller. Meeting last week end in April.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, C. M. Lund. *Secretary*, John Gillam, Box 1388, Fargo. Meetings, spring and fall.
- Northeastern New York Obstetrical and Gynecological Society.** (1935) *President*, Arthur D. Hengerer, Albany. *Secretary*, Raymond L. Rhodes, 15 W. Notre Dame St., Glens Falls, N. Y. Meetings, third Thursday of January, April, and October.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Delbert G. Smith. *Secretary*, Daisy G. Cotten, 525 N. W. 11th St., Oklahoma City. Meetings, February 9, April 13, May 5, 1955.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Leo T. Heywood. *Secretary*, W. Riley Kovar, 1120 Medical Arts Bldg., Omaha 2. Meetings, third Wednesday, January, March, May, September, and November.
- Oregon Society of Obstetricians and Gynecologists.** *President*, C. Louise Clancy. *Secretary*, Melvin W. Breese, 1340 S. E. 80th Ave., Portland 16. Meetings, third Friday, October through May, except December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Henry A. Stephenson. *Secretary*, Donald W. DeCarle. Meeting, The Lodge, Sun Valley, Idaho, Oct. 6-9, 1955.
- Pacific Northwest Obstetrical and Gynecological Association.** (1947) *President*, J. E. Harrison. *Secretary*, Earl L. Hall, 1220 Central Ave., Great Falls, Mont. Meeting, Empress Hotel, Victoria, B. C., May 15-18, 1955.
- Philadelphia, Obstetrical Society of.** (1868) *President*, J. Robert Willson. *Secretary*, Paul A. Bowers, 2031 Locust St., Philadelphia 3, Pa. Meetings, first Thursday, October through May.

- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, William E. Gibson. *Secretary*, John C. Hughes, Schenley Park Apts., Pittsburgh 13, Pa. Meetings, first Monday, October through May, except January.
- Portland Society of Obstetricians and Gynecologists.** (1928) *President*, Kenneth J. Scales. *Secretary*, Gerald E. Kinzel, Medical Dental Bldg., Portland 5, Oregon. Meetings, fourth Wednesday, September through May.
- Queens Gynecological Society.** (1948) *President*, George Schaefer. *Secretary*, Joseph A. Gaetane, 147-15 46th Ave., Flushing, N. Y. Meetings, second Wednesday, October, December, February, and April.
- Rochester Obstetrical and Gynecological Society.** (1939) *President*, Fred J. Fumia. *Secretary*, Joseph Cooney. Four meetings yearly.
- St. Louis Gynecological Society.** (1924) *President*, J. Russell Vaughan. *Secretary*, Eugene G. Hamilton, 8505 Delmar Blvd., St. Louis 24. Meetings, second Thursday, October, December, February, and April.
- San Antonio Obstetrical and Gynecological Society.** *President*, G. G. Passmore. *Secretary*, Frank M. Posey, Jr., 640 Moore Bldg., San Antonio. Meetings, first Monday of the month.
- San Diego Gynecological Society.** (1937) *President*, George H. Derieux. *Secretary*, Wayne B. Henderson, 2109 5th Ave., San Diego, Calif. Meetings, as announced.
- San Francisco Gynecological Society.** (1929) *President*, Ernest W. Page. *Secretary*, Edmund F. Anderson, 2445 Ocean Ave., San Francisco 27, Calif. Meetings, second Friday, October through April.
- Seattle Gynecological Society.** (1941) *President*, C. S. Fine. *Secretary*, John Clancy, 1010 Boylston, Seattle, Wash. Meetings, third Wednesday of each month, except summer months.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, Jack Parker. *Secretary*, Lawrence L. Hester, Jr., 16 Lucas St., Charleston 16. Meeting, spring.
- Southwest Obstetrical and Gynecological Society.** (1951) *President*, Celso C. Stapp, El Paso, Texas. *Secretary*, Zeph B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz. Annual meeting, Oct. 28-29, 1955, El Paso, Texas.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, G. F. Goff. *Secretary*, Carey Hiatt, 815 Fifth Ave., Ft. Worth. Annual meeting in February.
- Utah Obstetrical and Gynecological Society.** (1948) *President*, Morgan S. Coombs. *Secretary*, Von G. Holbrook, 508 East South Temple, Salt Lake City 2. Meetings, second Tuesday of October, December, March, and May, or as announced.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Eugene S. Groseclose, Lynchburg. *Secretary*, Chester D. Bradley, 2914 West Ave., Newport News. Meetings, April and October.
- Washington Gynecological Society.** (1933) *President*, Russell Jon Jansen. *Secretary*, Edmund F. Daley, 1835 Eye St., N. W., Washington, D. C. Meetings, October, December, January, March, and May.
- Washington State Obstetrical Association.** (1936) *President*, L. Bruce Donaldson. *Secretary*, Glen G. Rice, 805 Medical Dental Bldg., Seattle 1. Next meeting, Seattle, Wash., Sept. 24, 1955.
- West Texas Obstetrical and Gynecological Society.** (1954) *President*, J. R. Roden, Midland. *Secretary*, D. D. Wall, 234 W. Beauregard Ave., San Angelo. Meetings, twice yearly.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Dean D. Willson, Fond du Lac. *Secretary*, William V. Luetke, 1023 Regent St., Madison 5. Meetings, May and October.